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# THORACIC SERIOSCOPY[1]

## METHOD OF STUDY FOR PLEURO-PULMONARY LESIONS

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SERIOSCOPY of the thorax, according to the method which I have perfected, consists in taking, under specified conditions, four stereoscopic roentgenograms of the thorax. The four films are examined while superimposed one over the other in the same negative viewing box. By causing them to slide synchronously one over the other, the different thoracic planes, superimposed from the front backward, are successively brought into evidence, and at the same time one reads on a dial graduated in centimeters the depth of each of the planes examined.

### PRINCIPLE OF SERIOSCOPY

The principle of this general method of examination, conceived by Ziedses des Plantes, is made clear by the accompanying optical diagram (Fig. 1). Let us suppose that a stereoscopic roentgenogram is made of two grains of lead, $A$ and $B$, placed at different depths with relation to the plate (or film). With the anti-cathode at $F_1$ we have on one of the films two images, $a_1$ and $b_1$; when the anti-cathode is shifted to the position $F_2$ we find on the second film two images—$a_2$ and $b_2$. With the two films superimposed as in the figure, if they are made to slide one on the other in the direction of the arrows, $a_1$ and $a_2$ are first brought into coincidence to yield a clear image of $A$; at this moment only the points included in the plane passing through $A$ and parallel to the film give a clear image. It is only with a greater displacement that $b_1$ and $b_2$ can be brought into coincidence to yield a clear image of $B$ and of the plane passing through $B$. The degree of displacement is related to the distance between the object and the plate (or film).

This distance can readily be evaluated in centimeters (See Fig. 2). On the left side of the diagram is represented a scale composed of a block of wood in which are included lead figures superimposed at a distance of one centimeter one from the other. Let us assume that the figure 8 is comprised in the plane passing through $A$, and the figure 4 in the plane passing through $B$; at the moment when $a_1$ and $a_2$ are in coincidence, the two figures, 8 and $8_2$, are also in coincidence, giving a clear image of the figure 8. The same is true for figure 4 which is clearly defined when $b_1$ and $b_2$ coincide. Thus, at the moment when we can clearly see a lesion in the negative viewer, we can read simultane-

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ously the distance in centimeters which separates the lesion from the film.

In practice, in order to obtain a clear image of a single plane, the other planes yielding blurred and undiscernible images, to take the successive roentgenograms at exactly the same moment of respiration.

My "cardio-respiratory selector" has enabled me to do this very simply because its object is, precisely, to take in succession

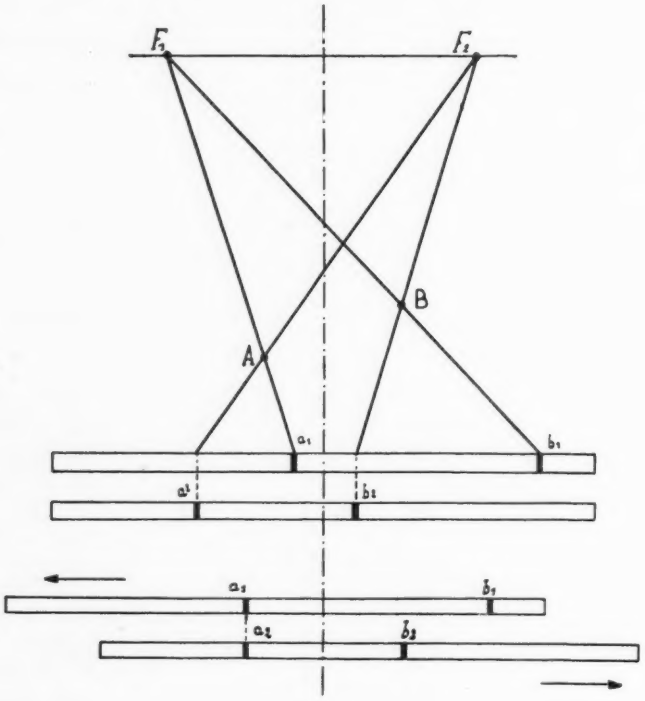


Fig. 1.

a single stereoscopic roentgenogram is not sufficient; two pairs of stereo-roentgenograms should be taken in succession, with the axes of shift of the tube perpendicular to one another.

### THORACIC SERIOSCOPY

The plane by plane study of lesions of the respiratory apparatus and the determination of their depth have seemed to me the most valuable indications for serioscopy, but the thorax offers for this method a special difficulty by reason of the variation in its form and volume during respiration. It is impossible to prolong respiratory apnea sufficiently to allow the taking of the four films, yet it is essential many roentgenograms at the same time of respiration or during a cardiac cycle, the patient being fitted with a pneumatic belt which, on respiration, governs the taking of the roentgenogram at the chosen moment. But since it comprises an amplifier, this apparatus is slightly complicated. Pulmonary serioscopy can utilize a more simple apparatus. For the latter method, therefore, I have had constructed a very simple "respiratory trigger" (Fig. 3).

This device comprises a U-shaped mercury manometer, the two branches of which are of different caliber. The larger branch receives the pressure variations of a pneumatic belt fitted to the patient. In the smaller branch are produced oscillations

of the column of mercury which are synchronous with the movement of respiration. A metal rod extends into the tube and, by means of a rack and pinion, this rod can be pushed down, more or less, into the tube; the patient to breathe freely while observing the oscillations of the mercury column which are made clearly visible by special lighting. At the moment when the mercury has left the contact rod, it is only

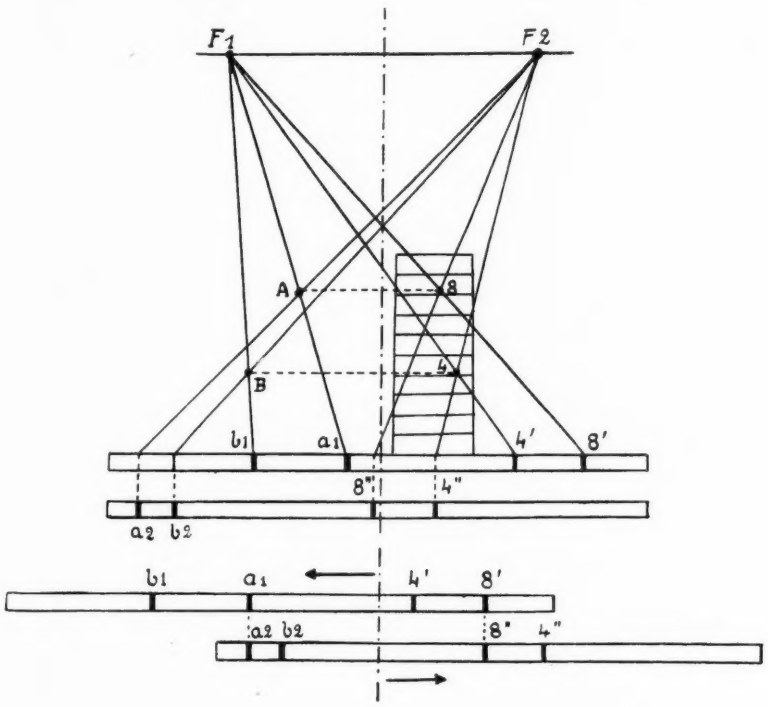


Fig. 2.

an electrical contact is thus established in a system supplied by the circuit, and this comprises a compacity connected in series with a metal oxide rectifier.

A sensitive relay mounted in series with the contact of the mercury manometer transmits the impulses to the trigger circuit of the roentgenologic apparatus through a locking relay. The purpose of the latter is to prevent any further release after the film has been taken.

To use the apparatus all that is necessary is to regulate the position of the metal rod so that electrical contact will be made at the selected moment of inspiration. Once this has been set, it is sufficient to allow necessary to press on a rubber bulb to close the circuit for the roentgenogram to be made at the following inspiration, at the moment when the next electrical contact will be made. Thus many successive roentgenograms can be taken at precisely the same moment of inspiration.

In addition to the foregoing, the apparatus also comprises an invertor which, by suitable setting of the contact rod, would permit the film to be taken at the end of expiration.

## TECHNIC OF FILM EXPOSURE

The patient, fitted with the pneumatic belt connected to the release, is placed in a

standing position as for an ordinary thoracic roentgenogram, behind the usual vertical chassis and is immobilized by a strap and

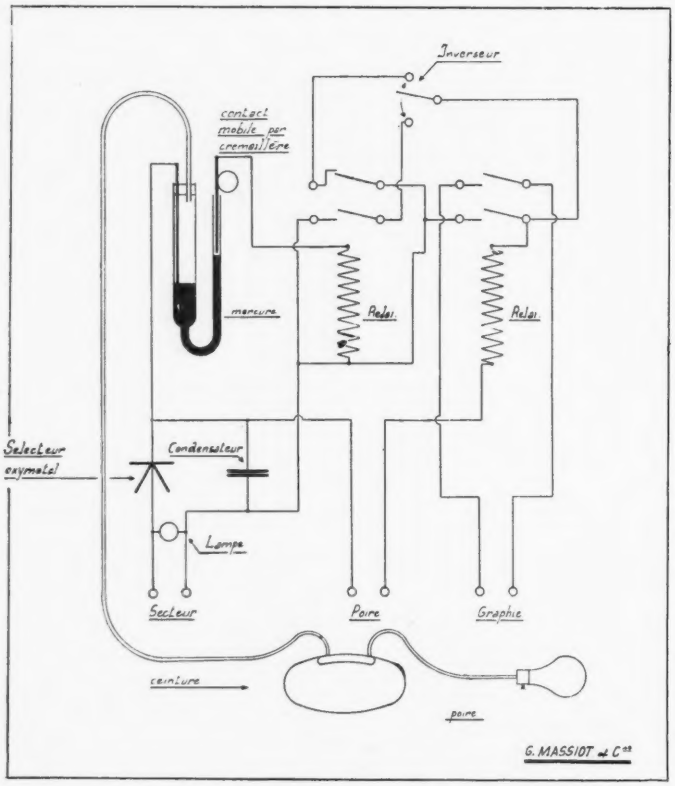


Fig. 3. Mounting diagram of the respiratory release of Cottenot.

by two arms with pads pressing against the shoulders (Fig. 4). The chassis is equipped with: (1) a bakelite plate inserted in the bottom of the cassette carrier, bearing two grains of lead, the image of which will serve as film indicators; (2) stops for the horizontal and vertical shifts of the tube.

After roentgenoscopic centering, the four roentgenograms are taken at a distance of 1.40 meters, the tube being successively shifted 14 cm. to the right, to the left, upward, and downward. The films, 30 × 40 cm. in size, are arranged with the maximum diameter in the horizontal plane for the first two, and in the vertical plane for the last two.

As has already been pointed out, quiet respiration on the part of the patient operates the release; the exposure for each film is one-third of the normal exposure; it is, therefore, very short, being approximately 0.5 second.

### EXAMINATION OF THE SERIAL FILMS

The serioscope on which the films are examined is a negative viewing device with powerful lighting, and on which slide four film carriers with synchronous and symmetrical displacement. One of the films is fixed on each of the carrier slides (Fig. 5). Thus, by the turn of a screw, the four films superimposed in the negative viewer can

slide one over the other in synchronism, each film being displaced in the same direction as that of the tube during exposure of the film (to right, to left, upward, and downward).

The screw which governs the shifting of the films also moves a needle in front of a dial, and the serioscopic examination of the scale with lead numbers has permitted standardization of the serioscope (for a focal distance of 1.40 meters and a shift of 14 cm.). The dial has thus been graduated in centimeters. The films are mounted on the serioscope in such manner that, with the needle at zero, the four images of two grains of lead arranged at the bottom of the cassette carriers coincide. By turning the shift screws we can explore successively an

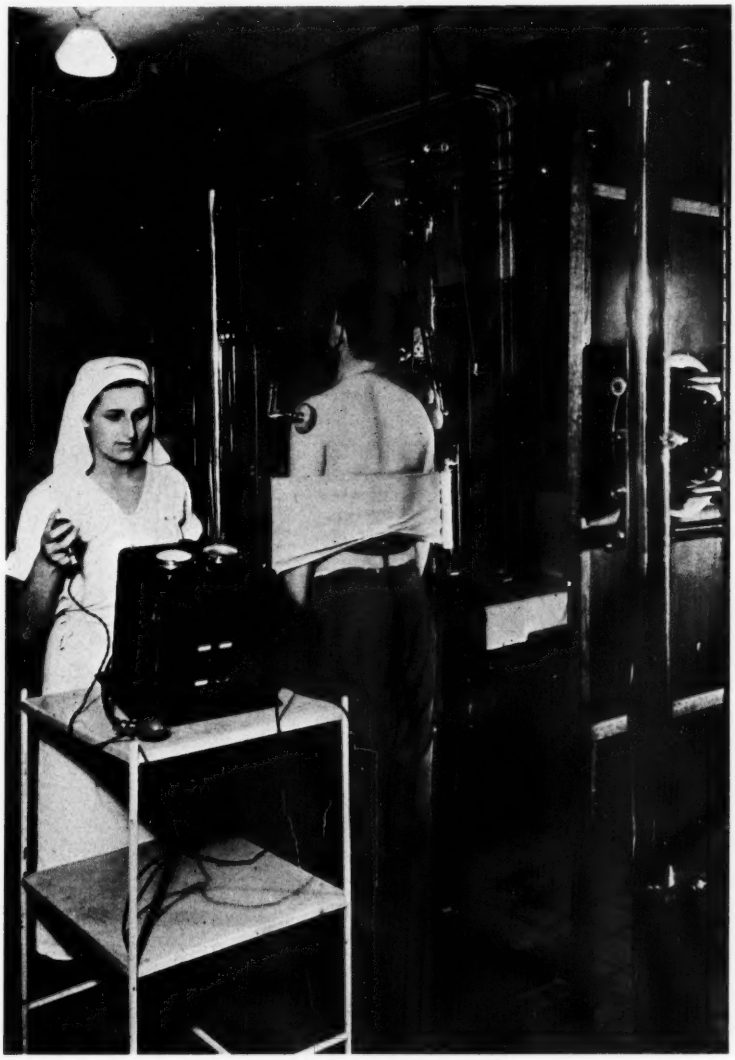

Fig. 4. The taking of a thoracic serioscopy.

infinity of thoracic planes superimposed from the front backward through the entire depth of the thorax, each plane examined giving a clear image while the other planes are blurred, and the needle indicates in succession the depth of the explored planes.

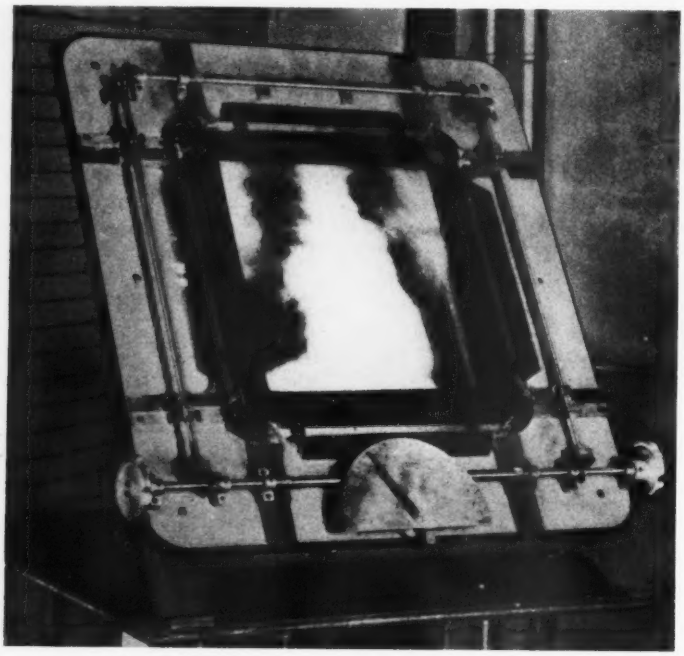

Fig. 5. Four films mounted in the serioscope.

### RESULTS OF THORACIC SERIOSCOPY

Serioscopy is interesting from two points of view: (1) it enables one to recognize and to identify lesions of the pleura or lung, which simple roentgenography does not bring out clearly; (2) it automatically gives in centimeters the distance which separates the lesion from the thoracic walls, —valuable information for the surgeon who must operate for an abscess of the lung, perform a thoracoplasty for tuberculous cavitation, or separate adhesions in pneumothorax.

Thus in cases encountered so frequently, in which silhouette roentgenography yields only uncertain information, the surgeon can accurately select the best surgical approach and may learn the depth at which the lesion may be encountered.

Some cases examined are as follows:

*Tuberculous Foci.*—(*a*) Silent cavity, expectoration of bacilli, doubtful roentgenography; serioscopy showed the cavity. (*b*) Expectoration of bacilli, negative auscultation; roentgenography showed the indefinite image of a cavity near the hilus. Serioscopy revealed the cavity, far back, behind the pulmonary vessels. (*c*) Expectoration of bacilli, negative auscultation; the roentgenographic appearances were uncertain. Serioscopy showed a tuberculous focus situated behind the left ventricle of the heart.

*Pneumothorax.*—(*a*) Serioscopy reveals a cavity situated in the lower lobe of the left lung. (*b*) Tuberculosis with cavitation. The first-stage of a thoracoplasty has been performed. Before the second-stage operation, the surgeon wanted to know the dimension and the situation of the cavity.

Serioscopy showed the very elongated cavity occupying the whole depth of the thorax (Fig. 6). (*c*) Right pneumothorax with apical adhesion. The adhesion is situated 6 cm. behind the clavicle, 4 cm. in front of the posterior costal arches, and has within it an elliptical cavity.

*Abscess of the Lung.*—Three abscesses about which profile roentgenography did not furnish any information. Serioscopy made it possible to localize them. (*a*) Abscess of the left lung shaped like a "brioche," 1 cm. from the anterior thoracic wall. Result confirmed by the surgeon. (*b*) Abscess in the right axillary region. Roentgenography did not show any cavity. Serioscopy showed three cavities and localized the abscess 14 cm. from the anterior wall, 3 cm. from the posterior wall. Healed without operation. (*c*) Abscess at the right base; serioscopy showed it far posteriorly, 2 cm. from the posterior wall; and this was confirmed by the surgeon.

*Hydatid Cysts.*—Two hydatid cysts of the right lung, with fluid level. These levels were in the case of the external cyst (posterior), 2 cm. from the posterior wall, and in the case of the internal cyst 5 cm. from the posterior wall.

Fig. 6. Serioscopy of a bilobed cavity after the first stage of a thoracoplasty; the plane of view passes 3.5 cm. from the posterior thoracic wall.

*Hyperostosis of a Rib.*—Anterior roentgenography showed a small, round shadow invisible in profile. Serioscopy shows that the hyperostosis affects the inferior border of the eighth rib on the right side.

# X-RAY DIAGNOSIS OF COMPLETE AND PARTIAL ACUTE INTESTINAL OBSTRUCTION

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From the Department of Radiology, Jewish Hospital

THE successful treatment of acute intestinal obstruction is directly proportional to the frequency of early diagnoses. We believe that the radiologist is in a position to diagnose correctly early cases of obstruction when the clinician may be in doubt even after thorough physical examination. Normal digestion and assimilation are interfered with in ileus by an alteration of peristalsis, secretion, and absorption; this is productive of accumulation of gas and fluid in the obstructed loops, with a resultant characteristic roentgenographic appearance of the abdomen on scout x-ray films. Seulberger, Brandes, and Roth (10) have shown experimentally that there is decreased absorption from the intestinal tract in ileus due to the hypertonicity of the bowel contents. Increased secretion, decreased absorption, and blocking of the intestinal contents in its passage to the colon account for intestinal distention in both mechanical and adynamic ileus. Ochsner (8) has proven that strangulated obstruction can be demonstrated by x-ray in one hour and a simple obstruction within three hours. According to the author, accumulation of gas is the first sign rather than gas and fluid. The films of approximately one hundred patients with symptoms of an acute "surgical belly" were studied. They naturally fell into the following group classifications: acute complete intestinal obstruction of small bowel; partial intestinal obstruction of small bowel; acute complete intestinal obstruction of colon; partial intestinal obstruction of colon; dynamic ileus (pre- and post-operative); control group (biliary colic, renal colic, acute appendicitis, etc.).

The anatomical distribution and grouping of coils of the small intestines, based on the embryonic studies of Mall and the clinical and radiologic work of Lewis Gregory Cole (3), fall into six divisions. (The small intestine begins with the duodenum and ends at the ileocecal valve.) The six groups are as follows: (1) The duodenum—situation largely retroperitoneal; (2) lies in the left hypochondrium and assumes a transverse direction; (3) lies transversely in the left lumbar within the pelvis; (4) lies vertically in the umbilical and upper hypogastrium; (5) lies vertically in the right lumbar area; (6) lies vertically in the right iliac fossa, false pelvis, and lower hypogastric area.

It is quite evident that, in any such grouping, owing to the massing, general distention, and displacement of the loops, picking the site of the obstruction is often wellnigh impossible. In the consideration of flat plates, it is very important to inspect films of all quadrants with a view to ruling out neurogenic, biliary, and renal calculi.

The first x-ray signs in an incipient case of ileus of mechanical origin are the presence of trapped gas and what is termed the "hairpin turn" (Fig. 1). A collection of gas in a dilated loop of the small bowel which, on successive films at hourly intervals, appears in the same loop, with or without further accumulation of gas in proximal loops, is, in our opinion, evidence of an oncoming ileus (Fig. 2). Furthermore, a dilated "hairpin turn" in the small bowel is the beginning of the so-called "step-ladder appearance" of massed superimposed loops of small intestines, and in its presence one must suspect a developing ileus (Fig. 3). These two findings have held true to this time and are to be viewed as definite signposts or red lights of warning. At this stage we do not know as yet whether we are dealing with partial or incomplete obstruction; such cases should be x-rayed at hourly

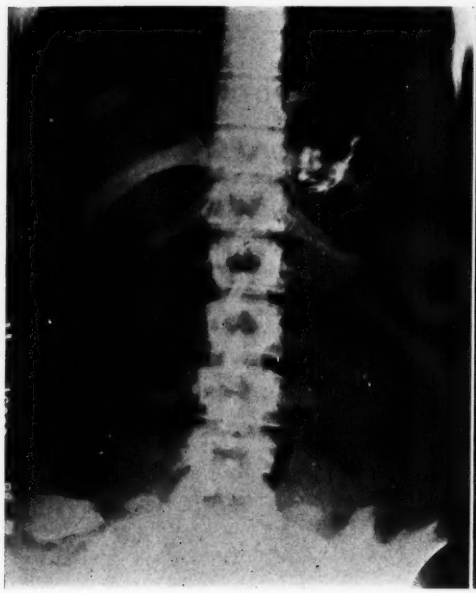


Fig. 1.

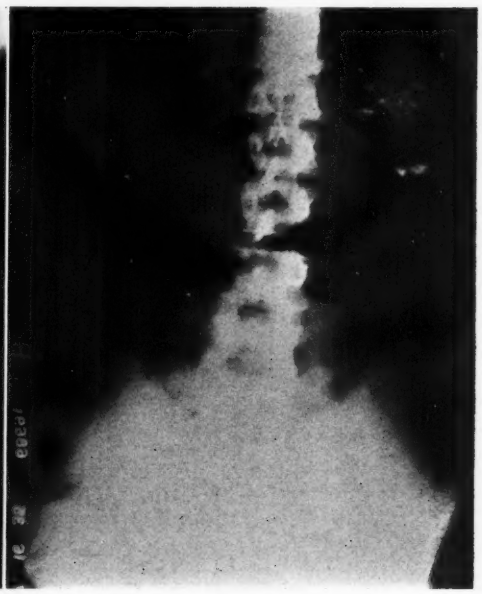


Fig. 2.

Fig. 1. Observe distention of gas in isolated small intestinal loops.
Fig. 2. Note "hairpin turn" and accumulation of gas in isolated loops at re-examination two hours later.

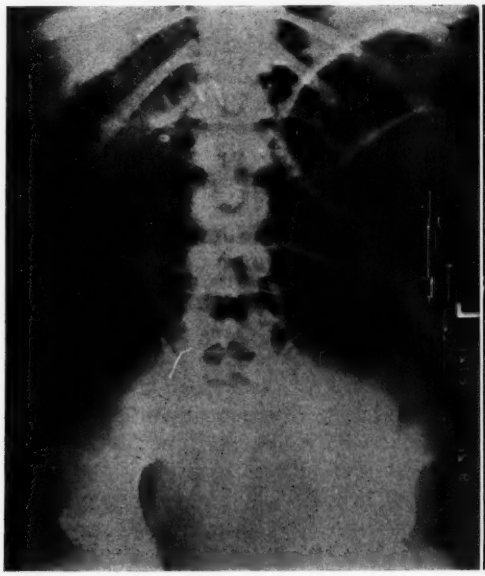
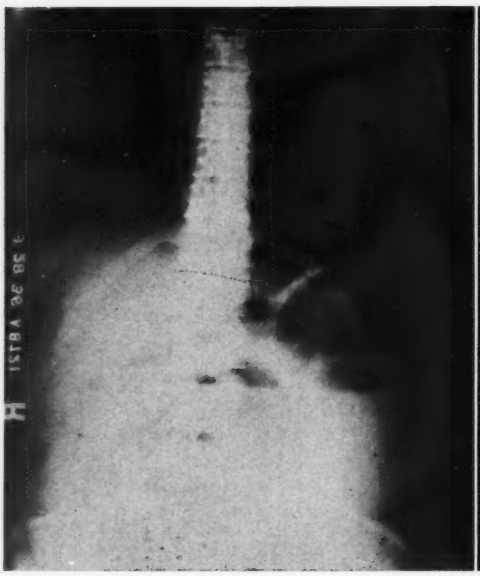


Fig. 3.

Fig. 4.

Fig. 3. Typical appearance of ileus: "step-ladder appearance," super-imposed dilated loops, marked valvulæ conniventes, and "hairpin turn" all indicate mechanical obstruction.
Fig. 4. Note that in morphinization of bowel the distribution of intestinal gas simulates the pattern observed in intestinal obstruction. Presence of gas in ileum and colon aids in excluding diagnosis of intestinal obstruction.

intervals over a period of from six to seven hours, and if the accumulated gas does not pass onward into the large intestine the diagnosis of partial ileus can be made with



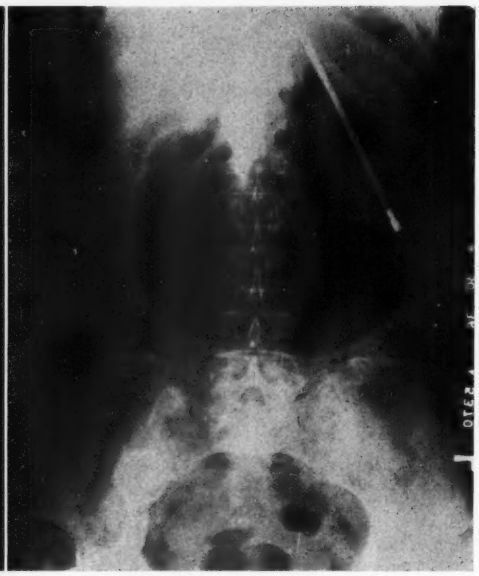


Fig. 5. Fig. 6.

Fig. 5. Observe multiple fluid levels in upright position—a late sign of ileus.
Fig. 6. Subhepatic abscess. Note marked gastric distention and absence of intestinal dilatation. A radiopaque shadow in subhepatic area. These findings are strongly suggestive of a subhepatic collection of pus or fluid.

a fair degree of accuracy. It is inadvisable in such cases to wait for the development of a typical "step-ladder appearance."

The significance of intestinal gas within both the small intestines and colon is as follows: If the colon is dilated from rectum to cecum and there is to all intents and purposes only a little air in the small bowel, then small intestinal obstruction can be excluded, and with the exception of rectal obstruction, colonic obstruction also.

Tremendous dilatation of the colon or part of it associated with fluid levels in the absence of small intestinal gas is *per se* indicative of large intestinal obstruction. The differentiation of large and small bowel is not always simple; the presence of haustrations identifies the large bowel. In the absence of this distinguishing feature one should keep in mind the central lateral distribution of the colon when viewed in the postero-anterior roentgenogram.

A consideration of the physiology of the ileocecal valve and sphincter enables one to correlate the above findings. According to Alvarez (1), the ileocecal sphincter acts as a barrier to most of the movements and contents of the ileum. By the folding of the muscle layers, contractions are led into a blind pocket where they are lost. Luciani (6) claims that peristalsis in the small bowel is not a continuation of that in the colon. The cecum, therefore, is a reservoir due to low irritability. The anemias of ileocecal lesions (tuberculosis, malignancy, and granuloma) are due to patency of the ileocecal valve, with rapid emptying of the contents of the ileum into the cecum resulting in faulty absorption. Regurgitation of bacteria, lodging normally in the cecum, into the ileum, produces fever, infection, and diarrhea. Thus, the ileocecal valve facilitates the diagnosis of ileus through its normal function as a sentinel between the small and large bowels. It is of interest to note that obstruction in the sigmoid may yield marked cecal distention and in some cases even cecal gangrene. As indicated by Case (2),

Fig. 7.

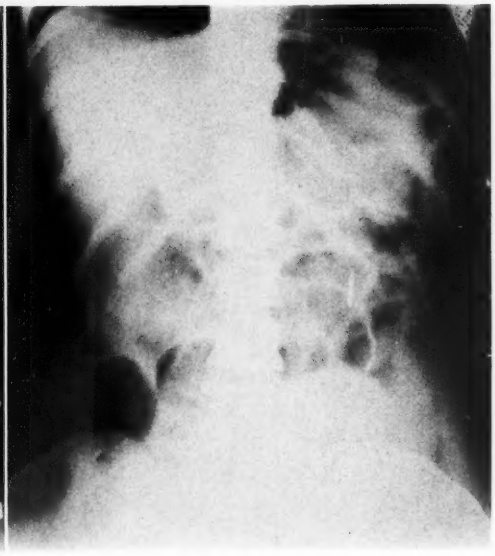


Fig. 8.

Fig. 7. Adynamic ileus. Differentiation from mechanical obstruction impossible but coils are often wider than in true mechanical obstruction.

Fig. 8. Mechanical intestinal obstruction. Segmented distribution of intestinal loops limited to upper abdomen and collapse of bowel distal to obstruction.

this curious finding is due to reversed peristalsis, predominant in the right colon, which may become exaggerated when originating in a tonic contraction ring in the sigmoid. Thus the cecum is caught between Scylla and Charybdis, suffering consequences even though far removed from the actual obstruction. The ileocecal sphincter is subject to the gastro-ileac reflex and contracts on stimulation of the pyloric sphincter. Distention of the stomach, duodenum, and ileum are accompanied by the same phenomenon, accounting partly for the absence of colonic gas in small bowel ileus (Henrichsen and Ivy, 5).

Morphine produces a general atonicity of the intestinal tract so that the effects of morphine may be manifested by large accumulations of gas both in the colon and small bowel. This gaseous distribution enables one to differentiate morphinization from ileus even in the presence of a pseudo-step-ladder appearance (Fig. 4).

Fluid levels in the obstructed bowel are comparatively late signs of obstruction and are due to intestinal hypersecretion (Fig. 5). The higher the site of obstruction the greater the amount of fluid present. Morton and Sullivan (7) have studied the amounts of fluid secreted in obstructed loops of duodenum, which are vastly larger than in the ileum, with a consequent greater degree of distention in high obstruction. One of the causes of this discrepancy is the proximity of the duodenum to the gastric, pancreatic, and hepatic sources of secretion. Thus, marked distention of loops of small bowel points to a high obstruction. Increased fluid content means increased intra-enteric pressure and results in a higher mortality rate when the ileus is high. The work of Dragstedt, Lang, and Millet (4), on the variation of the intramural blood supply in various segments of the bowel, accounts for the ease of compressibility of duodenal blood vessels as compared to colonic vessels, lending a physiologic basis for the well-known earlier distress in small bowel obstruction.

The massing of dilated coils in the typi-

Fig. 9.

Fig. 9-*A*.

Fig. 9. Observe marked distention of bladder displacing large bowel upward. Patient's symptoms due to large bowel obstruction and urinary retention.

Fig. 9-*A*. Same case shown in Figure 9. Opaque enema reveals a volvulus at the hepatic flexure. Ascending colon and cecum are involved in the bowel torsion.

cal step-ladder is also a late sign of obstruction (Fig. 6). The presence of striations in the mucosa indicates jejunal obstruction, while the ileum is relatively free of valvulæ conniventes. Duodenal or jejunal obstruction due to subhepatic collections is typified by marked distention of proximal small intestinal loops and gastric dilatation. We were thus able to diagnose a subhepatic abscess following cholecystectomy, producing an acute abdomen (Fig. 7).

The differentiation of adynamic ileus, peritonitis, and mechanical obstruction may be impossible by roentgenography alone (Fig. 8). However, in cases in which the intestinal distention is segmented and occupies only one quadrant of the abdomen, a mechanical obstruction may be inferred since the bowel distal to the site of obstruction is collapsed. Dynamic ileus is diffuse and generalized and usually presents marked bowel dilatation. Peritonitis, which is secondary to a ruptured viscus, may be diagnosed by finding subdiaphragmatic collections of gas.

Carcinomatosis has been diagnosed roentgenologically by observing x-ray features of obstruction plus a generalized haze throughout the abdomen, coupled with fading or complete blotting out of the ilio-psoas lines. A generalized haze without abnormal intestinal loops is often due to ascites or large collections of intraperitoneal blood, such as traumatic lacerations of the liver and spleen.

It is self-evident that enemas administered prior to roentgen-ray examination may produce fluid levels which may be falsely interpreted. It is, therefore, advisable to avoid use of enemas prior to routine survey film examination or to siphon off as much of the enema as possible so as to avoid the above diagnostic pitfall. While the roentgenologist may venture an opinion as to whether the obstruction is high or low, it is most often impossible to state categorically in what quadrant of the abdomen the obstruction is situated. It is helpful to remember that the majority of small intestinal obstructions are in the lower right quadrant.

Fig. 10.

Fig. 11.

Fig. 10. Illustrates the importance of a low film in obstruction due to incarcerated femoral hernia in obese individuals.
Fig. 11. Intussusception. Note the intussusceptum into the intussuscipiens.

Another important consideration that alters the x-ray picture of obstruction is the frequent use of the Wangensteen suction apparatus. This decompresses the intestinal tract and often causes a disappearance of the step-ladder pattern though not of the obstruction, leading to an erroneous x-ray diagnosis and a false sense of security on the part of the surgeon. It must be stressed again that isolated loops of the distended small bowel spell obstruction and indicate surgical intervention.

Mesenteric thrombosis is usually characterized by a "step-ladder appearance" usually limited to a few coils, which are only moderately distended. Mesenteric tumors usually produce partial obstruction as well as displacement of adjacent loops of bowel. The loops of bowel usually have a feathery ribbon-like appearance which fades out away from the tumor or cyst.

Isolated bands from epiploic appendices constricting the bowel may give false shadows simulating cysts. Again survey films help to exclude mechanical intestinal dilatation due to huge bladder dilatation such as is seen in tabes and neurogenic bladders. After evacuation of the bladder one should search for organic causes of obstruction such as volvulus. A case of this type is illustrated (Fig. 9).

Patients who have had previous gastrojejunostomies may present considerable gas in the jejunum, even in the absence of ileus, in the presence of functional nausea and vomiting. However, fluid levels are absent in these cases.

The simple expedient of including the femoral region in the survey film may reveal incarcerated femoral or inguinal hernias. This procedure is of value in obese individuals in cases in which such hernial sacs may be missed by the clinician (Fig. 10).

In all suspected cases of ileus, we routinely take three views, anteroposterior, postero-anterior, and upright. The anteroposterior view is usually most valuable in differentiating the large from the small bowel, possibly because of the superior films obtained in the supine position, since these sick patients are not always able to co-operate when lying prone.

It is still a speculation as to what the origin of the gas and fluid is in the ileus. Swallowing air during vomiting, fermentation, and putrefaction are undoubtedly all factors in gaseous distention, while intestinal hypersecretion accounts for intraenteric fluid levels.

Evacuation of the bowel distal to the point of obstruction may occur with the onset of symptoms. A history of defecation with the onset of symptoms without subsequent stools does not rule out a mechanical ileus. Hyperperistalsis is an early feature in intestinal obstruction and differentiates it from dynamic ileus or peritonitis. As pointed out by Ochsner, abdominal distention is a relatively late sign in acute ileus of the small bowel, particularly in a high obstruction, and the diagnosis should be made before this becomes marked.

One of the most common causes of obstruction in infants is acute intussusception which may either be ileocecal, ileocolic, or colic in type. The cause of the first two types may be a mobile cecum or a lymphoid hyperplasia about the ileocecal valve. These lymphoid nodules may encircle the ileum and project for some distance into the cecum, favoring invagination of the small bowel. Chronic intussusception is most commonly due to intestinal polyps or Meckel's diverticulum. The roentgen picture of intussusception is that of any intestinal obstruction, except for the fact that in some cases the head of the intussusception may be actually visualized on the x-ray films (Fig. 11).

Pregnancy deserves special mention in the discussion of obstruction. Occasionally, the gravid uterus approaching full term may produce large intestinal obstruction by mechanical compression of the sigmoid or a redundant descending colon, with all the typical x-ray findings of intestinal obstruction. Such patients should have a barium enema administered in the knee-chest position, which will readily allow the flow of the opaque mixture into the proximal colon. If unrelieved by this procedure, the possibility of utero-sigmoidal or uterocecal bands angulating the gut should be considered.

It is important to remember that ileus may be co-existent with another nonsurgical abdominal condition which may mask it, so that the former is brought to light only by a scout x-ray film and easily may be overlooked by the clinician. One such case in this series was an actively bleeding duodenal ulcer associated with distention, which the x-ray revealed to be an obstruction (mesentery thrombosis). Another was a case with typical symptoms of cholelithiasis, which x-ray films proved to be a small intestinal obstruction (following an old cholecystostomy).

## CONCLUSION

1. The diagnosis of acute intestinal obstruction can be made early by means of survey films of the abdomen.
2. The absence of "step-ladder appearance" does not rule out an ileus.
3. Patients should be examined in the prone, supine, and upright positions.
4. One should correlate the physical findings with the x-ray findings in attempting to differentiate dynamic ileus from mechanical obstruction.
5. In doubtful cases of obstruction, frequent x-ray examinations are essential for observing the progress of gas in the small intestine.
6. "Hairpin turns" and trapped gas in the small bowel are among the earliest signs of acute intestinal obstruction.

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# RADIOLOGY IN AMEBIASIS DIAGNOSIS[1]

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THE Republic of Colombia being a tropical country, the amebiasis produced by *Endamœba histolytica* is extremely frequent. It may be said that there is amebiasis in every city in Colombia, but its infection index—which has been impossible to determine exactly owing to lack of accurate statistical data—varies according to the several climatic zones. Cities located at an altitude of 2,634 meters, such as Bogotá, show a high percentage of amebiasis not only because great numbers of its inhabitants go out of town to lower or warmer climates, but also because contamination has been demonstrated in patients who have never been out of town. But as compared with other cities, the number of amebic patients is much smaller at an altitude of 2,634 meters, with an almost constant annual temperature of about 14° C. The number is much higher in cities located at sea level, like Barranquilla and Santa Marta, where the mean temperature is 27° C., and it seems still higher in climates having an altitude of from 800 to 1,600 meters above sea level with a temperature varying between 18° and 23° C. The difference between the last two groups is not considered great and mostly varies according to the localities studied, where infestation is naturally variable. All those places are invaded by amebiasis and comparison can be properly established only with cities more than 1,800 meters above sea level, where it is much less frequent. It has been my privilege to practise my profession in the city of Bogotá, capital of the Colombian Republic, and taking into account the above mentioned points, I have been led to consider the grade of amebiasis propagation in lower climates, since the statistical data which I have endeavored to collect demonstrate the enormous expansion of this infection among the inhabitants of Bogotá.

I refer to such data as the following: At the bacteriological laboratory of the Misericordia Hospital at Bogotá, which is exclusively devoted to children and where all patients are gratuitously cared for, it has been normal practice to make a coprologic examination for intestinal parasites in nearly all the patients. In 2,218 coprologic examinations, made between Jan. 1, 1936, and April 30, 1937, there were 173 patients with *Endamœba histolytica* cysts and 75 with vegetative forms of the same: that is, 248 cases of amebiasis in the patients examined. It may, therefore, be said that 11.18 per cent of the children who have come to the hospital were carriers of amebic germs.

At the laboratory of the San Juan de Dios Hospital, where the wards of the Faculty of Medicine are located, I also took information on 2,218 coprologic examinations carried out during the last months of 1936 and during 1937 up to June 15. I found 670 cases with amebic cysts and 151 with vegetative forms of the same. This means an infestation of 37.01 per cent. It must be pointed out that in the last named hospital a general examination is not carried out on every patient, the total number of whom is 1,400 per day, but only on those who are clinically suspected of having intestinal parasites.

At Professor Federico Lleras Acosta's private laboratory, 89 cases were found with amebic cysts or vegetative forms, in 500 examinations carried out during 1937 and the last months of 1936. The percentage is, therefore, 17.8. At another private laboratory, that of Professor Pedro J. Almanzar, there were 161 cases with amebic germs, in 1,604 coprologic ex-

[1] Presented before the Fifth International Congress of Radiology in Chicago, Sept. 13–17, 1937.

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aminations made from June 1, 1935, to May 30, 1937; that is, a percentage of 10.03. Attention must be drawn to the fact that to these last two laboratories go only individuals of intelligence and social standing who have been clinically suspected of an intestinal parasitism or who have undergone a complete examination and have especially asked for a coprologic examination, even if they are not suspected clinically. The last ones are, of course, much less frequent.

The total number of coprologic examinations mentioned amounts to 6,540, of which 1,319 showed amebic cysts or vegetative forms of the same; that is, 20.16 per cent positive examinations showing amebic germs.

The above statistical data reveal the frequency of amebiasis among the inhabitants of Bogotá, and as it is acknowledged that such disease is far more extensive at lower altitudes or in warmer climates, one cannot but speculate how frequent amebiasis is in the whole Colombian territory.

Now, all Colombian physicians are well aware of the frequency of amebiasis and hence their clinical knowledge of it is sufficiently sound to enable them to detect the disease in every case of an acute or chronic dysenteric symptomatology. At the same time, the protozoölogists who deal with its microscopic examination have a very good practice, and, therefore, we must credit the results of their examinations. But two other important points must be taken into consideration: the first one is the well-known fact that a single isolated coprologic examination with a negative result for amebic germs does not imply the absence of such parasites. It is necessary to make at least three consecutive examinations within one month in order to be quite sure. The second point to be considered is the percentage of patients who are carriers of *Endamœba histolytica* without dysenteric phenomena.

Since the symptomatology of amebiasis is exceedingly variable, the clinical knowledge of physicians dealing often with such disease, added to the data supplied by the laboratory, and the success obtained in several patients submitted to an antiamebic treatment (although the laboratory examinations were negative), are not altogether sufficient to enable one to detect all the patients who suffer digestive disorders due to an amebic infection.

The variable manifestations of amebiasis allow us to classify the disease into the following four groups: I. Amebiasis with dysenteric phenomena in acute period; II. Chronic amebiasis with recurrent dysenteric attacks; III. Chronic amebiasis with variable digestive disorders, without dysenteric phenomena: (*a*) with dysenteric antecedents, (*b*) without dysenteric antecedents; IV. Carriers of amebic germs without clinical symptoms.

The first two groups, the diagnoses of which are daily made from the clinical symptoms and laboratory test, are seldom sent in for a radiologic examination. Only a few dysenteric patients with recurrent attacks are thus examined between two consecutive periods, but as a general rule it is not customary to carry out a radiological examination on patients belonging to the first two groups above mentioned. On the other hand, very often patients who have no colitis symptoms come to x-ray laboratories with various digestive phenomena but mostly without suspecting amebiasis, and through a radiologic examination it has been possible to demonstrate the presence of such disease The last group, the carriers of germs, are identified only at an x-ray laboratory by experiment, since a patient having no disorder does not consult either the radiologist or the digestive tract specialist.

It is, therefore, the third group which usually comes to the radiological laboratory. And since the clinical examination has not brought amebiasis to evidence and since as a rule the patient does not remember whether or not he has had dysentery at some remote time, it helps greatly to find radiologic signs that may help toward the diagnosis of amebiasis.

In my own private laboratory at the

Marly Clinic I have found, in a total of 11,067 patients examined to date, 124 cases of confirmed amebiasis and 13 cases of probable amebiasis. Out of the total number, approximately 50 per cent were examined for the digestive tract, but it may be said that for the first 5,000 patients examined from April, 1923, to March, 1931, I had not had enough practice to be able to direct my diagnosis toward amebiasis, as I find only three patients classified under that disease during that time. The remaining 134 patients are between the numbers 5,000 and 11,067, that is, between March, 1931, and May, 1937. Therefore, among those last patients, half of whom were examined for the digestive tract, there were approximately 4 per cent with amebiasis diagnosis.

I must point out that during the last ten years I have made a most complete radiological examination on every patient who has come in for disease of the digestive tract. This means that if a patient comes to me or is referred to me for a simple gastric, vesicular, or intestinal examination, I make a thoroughly complete investigation of all his digestive tract. In each patient I study the gall bladder by the oral Graham-Cole method, using a single dose of tetraiodide. I make the examination at the end of 14 hours, before the patient has had anything to eat, and again at 20 hours, after the patient has taken his usual daily lunch. Later on I study the stomach and duodenum. After 6, 12, 24, and sometimes after 36 and 48 hours, following the ingestion, I study the cecum and colon, and if it is necessary, I finish the examination with an opaque enema. I have described the technics followed in my examinations because with these complete studies there is greater probability of detecting any amebic lesion in patients whose symptoms may be, for instance, exclusively gastric.

In order to verify the radiologic studies made during recent years in civil practice, and considering that acute or chronic cases with recurrent and dysenteric phenomena did not reach my laboratory, toward the end of last year I decided to make an experimental study on 25 patients, nearly all from the San Juan de Dios Hospital. The results thus obtained confirmed the previous knowledge thus far acquired.

## SCIENTIFIC LITERATURE

Having established the importance of radiology in the investigation of amebiasis, it is astonishing to find so little scientific literature on the subject. In 1924 (1) and again in 1928 and 1934 (2, 3), J. J. Vallarino stated that the amebic ulcerations of the colon produce "repletion defects" which may be clearly seen on a roentgenographic film. He pointed out some irregularities in the outline of the intestinal parts affected, whose most frequent locations are, first, in the cecum, then the ascending colon, and lastly in the sigmoid. Having had an extensive practice for several years in Panama, he came to the conclusion that the abnormalities pointed out, although not pathognomonic, are useful in practically every case to confirm later on the existence of amebiasis.

E. Speder has studied the matter since 1917, and of his three publications with which I am acquainted (4, 5, and 6) the last one (6) is a résumé of his 19 years of observation during a practice of radiology in an absolute tropical region like Maroc. He brings out the fact that in old amebic patients a single examination at the laboratory and one without previous preparation, shows amebic germs in only 20 per cent of cases, and that repeated laboratory examinations hardly show it in from 40 to 60 per cent of cases. He holds, therefore, that the radiologic aspects, which in certain cases are characteristic of an amebic colon in from 60 to 70 per cent of cases, should be sufficiently convincing to the practising physician to cause him to repeat the microscopic investigations or to insist on a trial treatment. He classifies the aspects of the amebic colon into several groups, according to the age and the degree of the infection, to the degree and nature

of the lesions, their distribution, and the transitory or permanent modifications carried out by *Endamœba* in the wall of the colon. He holds that only amebiasis is liable to produce lesions located at different segments of the intestine, with intermediate zones almost normal or at least less affected by the pathologic process. According to him, such distribution in foci or groups of foci is practically pathognomonic in amebiasis. He divides the radiologic forms into: *Soft*, similar to those observed in all diseases which produce mucous endocolitis, and *dry*, which are the most serious, and in about 70 per cent of cases, radiologically characteristic of parasitic colitis. He also describes the various clinical forms of non-dysenteric symptomatology. Lastly he points to the supra-cecal region, the superior third of the ascending colon, the cecum, the sigmoid, the descending colon, left third and then the right third of the transverse colon, as the favorite places, in the order mentioned, for amebic lesions.

K. Ikeda, in 1934 (7, 8), on the occasion of an epidemic of amebic dysentery in Chicago, found characteristic deformities of the cecum and ascending colon, by the roentgenological studies made in subacute or early chronic stages of the disease. The roentgenological data obtained by him are apparent shortening or contraction of the wall, with induration and filling defects in varying degrees. The appearance may vary considerably, depending upon the extent of the infection; in early cases the roentgenographic film shows little that is diagnostic and he considers that when the abnormalities found by him are confirmed by the x-rays, one has a greatly presumptive basis of amebiasis, even if there are no pathognomonic signs. He says, in summary, that roentgenologic study must be a guide in the diagnosis and treatment of amebiasis.

J. C. Bell (9) has also found peculiar deformities of the cecum in amebiasis and believes that, although such image can be seen in other diseases, the clinical history of the patient and the laboratory tests serve to confirm the diagnosis. He cites cases of seven patients studied by him and observed during treatment, to corroborate his conclusions.

H. M. Weber (10), speaking of those diseases in which dysentery is a prominent symptom, says that the pathologic changes detected by means of roentgenology in the intestines of amebic patients are essentially the same as those produced by other types of ulcerative colitis, except that the process seems to be one of comparatively diminished intensity and severity. He goes on to say that amebic ulcerative colitis has a fairly distinctive roentgenologic *look*, difficult to describe. In cases in which the signs of ulcerative colitis in the cecum and in adjacent regions without ileal involvement are preponderant, he points to the presence of unaffected loops of colon interposed between diseased regions. This same author (11), speaking about the radiologic identification of ulcerative colitis—in which are found narrowing and shortening of the intestine, mural thickening confirmed by increased resistance to palpation, diminished mobility and flexibility, and mucosal destruction revealed by marked changes of its relief—insists upon certain radiologic data which allow one to distinguish amebic ulcerative colitis from tuberculous ulcerative colitis and diplo-streptococcic colitis. Its frequent localization in the cecum; the extent of the ulcerative process beyond the site of primary involvement; the interposition of relatively unaffected segments; the fact that the shortening, narrowing, and destruction of the mucosa are little noticed; the relative mobility and elasticity of the intestinal wall; the lack of invasion of the ileum and finally the lesser intensity of the process as compared with other ulcerative colitis, are the data that he uses to make the differential diagnosis.

As seen from this study of the literature, all the authors agree that in the greater proportion of amebic processes there is a radiologic "look" which reveals itself, especially by the general picture of ul-

cerative colitis, accompanied by deformities in the outside shape of the segments most affected, without invasion of the ileum and leaving undamaged large intestinal segments.

Such a radiologic "look" is considered by all as suggestive of amebic lesions, but none of the authors claims the existence of a pathognomonic picture that allows the diagnosis to be made without the clinical and laboratory examinations or the trial treatment. Nevertheless, they unanimously agree that the radiologic study places the diagnosis on very sure basis.

## RADIOLOGIC SIGNS FOUND

Since I have included the whole digestive tract in the radiologic studies on which this report is based, it is advisable to present data referring to the function performed by the stomach, duodenum, ileum, liver, and gall bladder before describing the appearance of the cecum and colon.

*Stomach.*—Beside the variations that may be found in gastric motility and in some reflex spasmodic deformities which often present themselves in amebiasis, as in several other abdominal diseases, and whose variableness and lack of individualization for this disease do not permit taking them into account, it seems to me rather opportune to point out the frequency of gastric retention of a good amount of the barium meal at the end of six hours. This is caused, no doubt, by a retarded spasm of the pylorus, since in these patients there were found no signs of organic lesions that explained the retention, nor could there be detected any delay in gastric evacuation at the beginning of the examination.

*Gall Bladder.*—As a general rule, visualization of this organ in the films taken 14 hours after oral administration of the dye was normal with the exception of cases in which there was present also a cholecystitis not ascribable to amebiasis. However, in two of the observations which I present the gall bladder was not visible, precisely as in patients suffering from abdominal colics clinically classified as gall-bladder pains. The interesting aspect lies in the fact that through macroscopic and microscopic studies of the bile of these patients, extracted by duodenal intubation, no signs were found revealing the presence of gallstones nor of cholecystitis of other origin. To this must be added the fact that colic disappeared in those patients under antiamebic treatment. I only point out this fact, being unable yet to draw any conclusion from it.

*Liver.*—In the radiographic films of the hepatic region taken of these patients at the moment when the gall bladder was visible, I could often observe a relative increase of size of the liver as well as a good delineation of its total shadow, which could be attributed to an increase of density of this organ.

*Ileum.*—There was nothing worth mentioning in this segment of the intestine. I never found deformations that could be ascribed to amebiasis, and the retention therein found in those patients is explained rather by the delay in gastric evacuation. At any rate, it must be mentioned that such retention lasted for a maximum of 12 hours.

*Duodenum.*—I found no abnormality in this organ ascribable to amebiasis.

*Cecum and Colon Aspects: The Cecum-colon Transit.*—Although in many of the patients there is no disturbance in the time taken by the opaque substance to travel through the cecum-colon segment, I have observed in some of them variations which are worth mentioning. The first is the rapidity with which the first part of the opaque meal travels through the cecum-colon segment, as demonstrated by the fact that I observed it many times at the descending colon and even at the sigmoid and the rectum at the end of six hours. The location of this first part of the barium meal is in contrast with the delay of the last part of the meal, which remains at the stomach. The second observation is the retention for as long as 24, 36, 48, and even up to 72 hours of that same meal of which the first part travelled rapidly through a colon whose numerous and

visible haustral markings led one to expect that the evacuation would not take very long. In other cases the travelling time through the cecum-colon segment seems normal in the first 12 hours, but the delay in evacuation later is also very frequent, sometimes being accompanied by a ptosis of the transverse colon and the cecum, without any alteration at all in the position of the stomach.

*Cecum-colon Hypersegmentation.*—Perhaps the first radiologic sign which arouses suspicion of a possible amebic chronic infection is the considerable number of segmentations or haustral markings which are seen in the cecum, ascending colon, and more especially in the transverse colon, at the first observation made six hours after the ingestion. The number of these segmentations is nearly always above normal and such increase is observed at first sight. Speder has also noticed hypersegmentation, with the number of haustral markings reaching 26 or 28, when as a rule they do not go beyond 10 or 16 in non-amebic patients. This so-called radiologic "look" implies consequent narrowing of the colon. The same picture is again seen at examinations carried out 12 or 24 hours after ingestion, or even later, and such hypersegmentation may be apparent in the descending colon when it is well filled. When examination is carried out with an opaque enema, the radiologic aspect is not the same, and although numerous segmentations are sometimes seen they do not always give the same pictures. It is well to point out the fact that in some colon zones segmentations are almost normal.

*Hypersegmentation Variableness in the Cecum and Colon.*—To the radiologic picture which I have just described, it is important to add the marked inequality which exists nearly always—in cases in which such pictures are observed—in said segmentations. Some are far more intense than others, at varying distances one from the other, and in some places with circular and uniform narrowing. As a general rule, in the several examinations carried out after ingestion, the same narrowing and changes of outside shape are repeated at the same sites where they were clearly observed at the first examination.

*Unequal Distribution of Barium Meal along the Colon.*—It is a relatively common observation that the fore part of the opaque meal is distributed in zones quite isolated one from the other, often impregnating the mucosa and showing hypertrophy of folds. Such a picture would not be at all characteristic if it were not that in subsequent examinations one can see zones not occupied by barium which are nearly always the same ones, as if an explanation of this fact were furnished by an inflammatory stage located at determined segments.

*Diminution or Absence of Haustral Markings or Segmentations in the Cecum and Colon.*—This relative or almost absolute absence of segmentation is observed only by examinations after ingestion of those very few cases accompanied by ptosis of transverse colon, dilatation and wall atony, and whose amebic infestation started long ago. On the other hand, by injection of an opaque enema one can often see slight narrowing at certain colon zones, segmentations of variable length and small depth, reminding one of the picture of all ulcerative colitis with practically no amebic character.

*Induration and Atony of Colon Walls.*—In examinations made with injection of opaque enema there is frequently observed a uniform narrowing of the left part of colon with decreased elasticity of walls. And less frequent but not extraordinary is an atonic state of walls in old cases, with easy distention by the enema and with elasticity not only undiminished but rather increased.

*Aerocolia.*—The presence of gases in the colon, especially near the hepatic and splenic flexures, when there has been partial barium injection, is relatively frequent in those segments, but it has no value at all for diagnosis.

*Contours of Some Segments of Colon and Cecum.*—A careful study of the whole contour of cecum and colon is of great value and should be carried out repeatedly by

ingestion and also by injection of opaque enema. With such mindful study it is possible to detect the presence of isolated and relatively short zones ("saw-tooth" shaped, not too deep but very close to each other) which have no doubt a great diagnostic value and probably indicate ulcerations of mucosa at the sites where those zones occur. As a general rule, only one relatively short segment, which is doubtless the most affected, gives in all examinations made by ingestion or with opaque enema, the "saw-toothed" contours (seen in several cases presented) and to which I ascribe a great diagnostic value.

*Study of Mucosa Folds.*—Only in the experimental cases did I study imbibition of mucosa with "diagnotorine," and I was able to observe in several of them the abnormal distribution of folds and the edematous state, presenting ulcerations at proctoscopic examination. As I generally found this radiologic picture in the zone accessible to direct examination, I do not consider it of great practical interest.

*Radiologic Aspect in Dysentery, Both in Acute and Soon after Acute Stages.*—It is possible not to find any diagnostic radiologic signs at the beginning of acute amebiasis or in cases of minor intensity of dysenteric phenomena, but in the majority of such cases I have observed pictures similar to those seen in the other patients. I call attention to the lack of abnormalities in rectal and sigmoidal segments presenting ulcerations; to gaseous dilatation of those same segments in such cases as did not fill with barium, and to the considerable length of the sigmoid in some of them. Lastly, I must point out that patients examined in the acute stage ejected the opaque enema before complete injection of the colon was obtained.

*Location of Lesions.*—The presence of great intestinal segments not at all or little affected, the absence of lesions of the ileum, and the evidence of radiologically abnormal segments of cecum and colon are all characteristic of amebiasis. Such locations may be found from cecum to rectum; in this last case radiologic examination after ingestion or opaque enema does not help the diagnosis, even if ulcerations are numerous. As to frequency of location, I have seen that the descending colon and zones adjacent to the hepatic and splenic flexures are the most frequently attacked; afterward come the cecum and other colic segments.

## EXPERIMENTAL CASES

The 25 experimental cases are classified as follows:

| | |
|---|---|
| Normal after clinic, radiologic, and laboratory examinations | 3 |
| Amebiasis confirmed by laboratory, proctoscopic, and roentgenologic examinations | 16 |
| Amebiasis confirmed by laboratory and proctoscopic examinations but without any greatly apparent radiologic signs | 3 |
| *Coli ameba* dysentery with sound mucosa; roentgenologically normal | 1 |
| Old confirmed amebiasis with negative coprologic examination, mucosa ulcerations, and positive roentgenological signs | 1 |
| Old confirmed amebiasis with negative proctoscopic and laboratory examinations and positive roentgenologic signs | 1 |
| | 25 |

Clinically they are divided as follows:

| | |
|---|---|
| Normal | 3 |
| Amebiasis in acute stage | 6 |
| Chronic amebiasis in a recurrent attack | 4 |
| Chronic amebiasis with variable digestive phenomena and without dysenteric antecedents | 2 |
| Chronic amebiasis with variable digestive phenomena that began with an acute attack | 4 |
| Carrier of amebic germs without clinical symptoms | 1 |
| Amebiasis just after the acute stage | 2 |
| Old amebiasis apparently healed, without amebic cysts in the stools but with variable digestive phenomena | 2 |
| Dysentery in acute stage without other germs than *Coli ameba* | 1 |

The results of proctoscopic examinations are as follows:

| | |
|---|---|
| Unaffected mucosa in normal patients | 3 |
| Unaffected mucosa in chronic amebiasis | 2 |
| Unaffected mucosa in *Coli ameba* dysentery | 1 |
| Change of color of mucosa in chronic amebiasis | 3 |
| Edema and change of color of mucosa without ulcerations in chronic amebiasis | 3 |
| Amebic ulcerations of mucosa in acute and chronic cases | 13 |

The results of coprologic examinations are as follows:

| | |
|---|---|
| Normal without cysts or vegetative forms in the stools | 3 |
| Old amebiasis without amebic germs when examined | 2 |

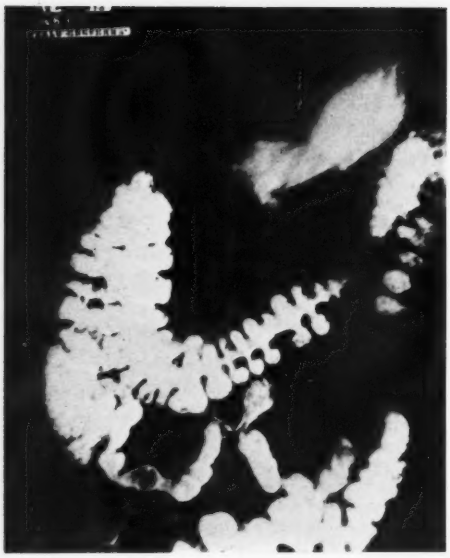

Fig 1

*Endamœba coli* ..... 1
*E. histolytica* cysts ..... 9
Vegetative forms of *E. histolytica* ..... 10

In the six acute cases, in the two in which the acute stage had just passed, as well as in the chronic case with dysenteric phenomena, there were found vegetative forms, and in all other chronic amebiasis cases there were found *E. histolytica* cysts.

SUMMARY OF SOME OBSERVATIONS

Case 9660. Amebiasis colitis with recurrent attacks. The patient had the last dysenteric crisis a year before examination. Since then he has been suffering from severe pain in the epigastric and hepato-vesicular regions, which passes away upon eating. On palpation at McBurney's point there is epigastric pain. Figure 1 was taken six hours after barium ingestion. Notice in it the six-hour gastric retention, colic hypersegmentation, irregular aspect of left part of transverse colon and of middle third of descending colon, the lower location of transverse colon, especially of its right half—with normal location of stomach—and the presence of fore part of barium meal at rectum after six hours. Twelve hours later there was ileal retention, and 24 hours later the whole opaque meal remained in the large bowel. Normal gall bladder

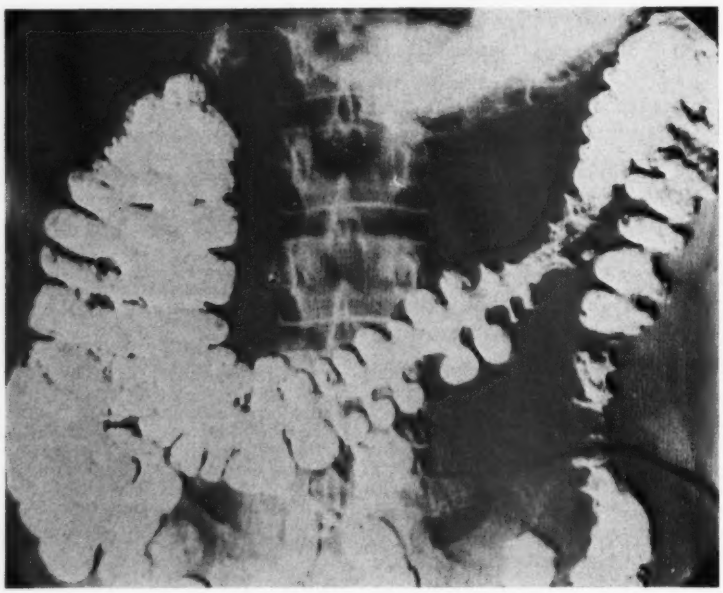

Fig. 1-*A*.

After examination there were amebic cysts present in the stools. Treatment: emetine, carbarsone, and stovarsol. The

patient recovered with this treatment and has not returned. (See also Fig. 1-*A*.)

Case 10382. Removal of appendix some years before. Six months before examination patient had amebic dysentery from

Fig. 2.

Fig. 3.

which he recovered completely with treatment. Consulted physician because of very strong abdominal cramps located in

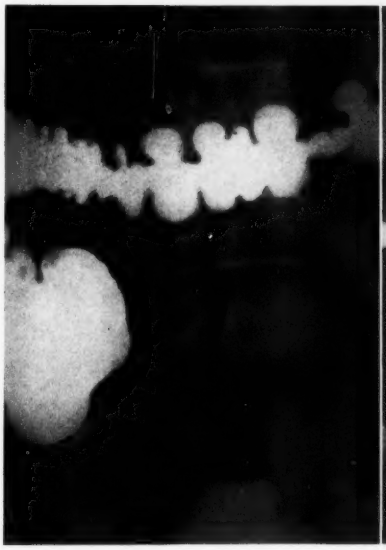

Fig. 4.

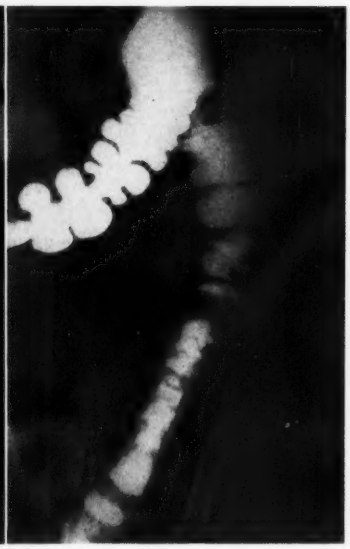

Fig. 5.

hepato-vesicular region. No colitis phenomena nor any amebic cysts found in the stools at time of examination (Fig. 2 after six hours' ingestion; Figs. 3 and 4 after 12 and 24 hours' ingestion, and Figs. 5 and 6 with opaque enema). Notice gastric retention at six hours and ileal retention at 12 hours, the small diverticula of ileum, the unequal hypersegmentation of transverse colon with spasmodic narrowing at its middle third, the small "saw-toothed" contours of the descending colon and its narrowing after enema injection, and the small quantities of barium distributed all along the

Fig. 6.

Fig. 7.

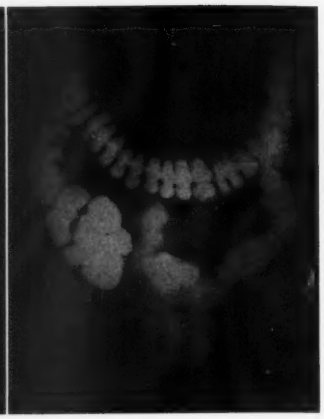

Fig. 8.

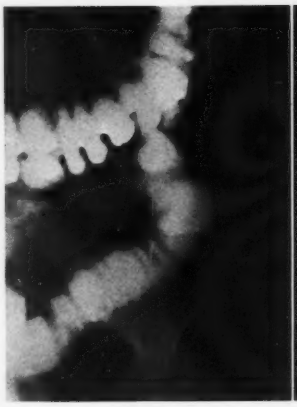

Fig. 9.

Fig. 10.

Fig. 11.

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Fig. 14.

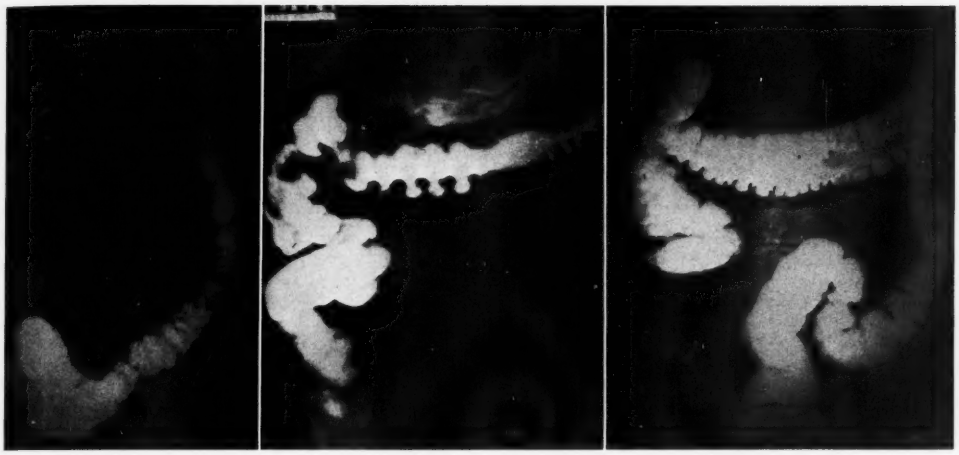

Fig. 15. Fig. 16. Fig. 17.

transverse and descending colon apparent at the six- and 24-hour examinations. The gall bladder was not visible by oral cholecystography. Bile examination after duodenal intubation did not reveal any abnormality. Presence of amebic cysts in stools after one month; increase of such cysts at the beginning of anti-amebic treatment. Cramps disappeared after two months' treatment.

Case 10363. Patient suffered for nine months from strong epigastric cramps which started during pregnancy. Miscarriage at six months and persistency of cramps after it. Old antecedents of colitis with mucus and painful phenomena but without diarrhea. The gall bladder was normal. Figure 7 shows films taken 12 and 24 hours after ingestion, and Figures 8 and 9 were taken at the same moment but with additional opaque enema. There was also gastric retention at six hours. Notice increase of haustral markings in cecum, ascending and transverse colon (very unequally distributed in the former), delay in colic transit in spite of hypersegmentation, narrowing of descending colon after enema, and "saw-toothed" contours of part of descending colon. Patient improved with anti-amebic treatment and has been well up to the present time.

Case 10264. This patient suffered for three months from strong epigastric cramps; pain all over right part of abdomen; had fever up to 38° C. two or three nights per week. There were very remote amebic antecedents. (Figure 10 was taken six hours after ingestion and Figures 11 and 12 were taken 12 and 24 hours, respectively, after barium meal and with opaque enema at the same time.) Note gastric retention at six hours; the colitis aspect in this film of transverse colon, with irregularity of contours, narrowing and shortening; the small "saw-toothed" contours of cecum and descending colon with narrowing of latter; unequal distribution of haustral markings in transverse colon seen at last examination, and flattening of hepatic flexure of colon due to compression by very large liver. Positive coprologic examination for amebic cysts; increased number of white cells and polynucleosis, with no eosinophiles. Normal gall bladder. Diagnosis: hepatic abscess of amebic origin at first, with amebic lesions at cecum and colon. The patient recovered under anti-amebic treatment.

Case 10486. Appendix had been removed; amebic colitis antecedents; two to three soft stools per day; epigastric pain and pain over the transverse colon. (Figure 13, taken 12 and 24 hours after

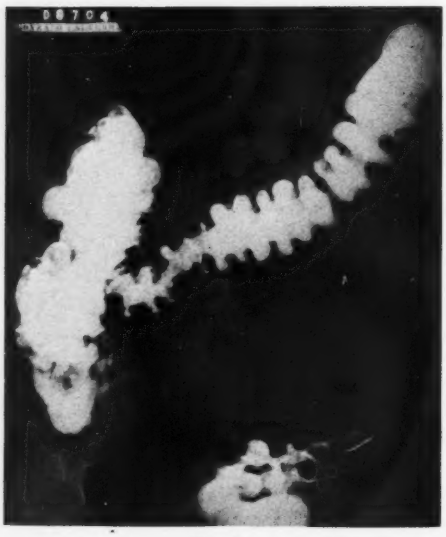

Fig. 18.

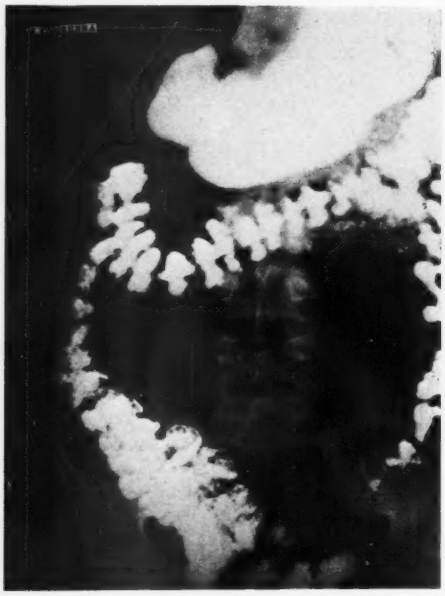

Fig. 19.

repeated barium ingestion and also with opaque enema.) Barium after 24 hours in the transverse colon. Gastric retention at six hours. Normal gall bladder. Notice narrowing and shortening of transverse colon and small "saw-toothed" contours with increased narrowing of left part. Several coprologic examinations made afterward confirmed the presence of amebic cysts. Extended treatment with Ravaut paste, potassium iodide enemas, and eme-

Fig. 19-*A*.

tine. Improved but not completely recovered.

Case 9713. Without dysenteric phenomena or amebic antecedents. Pain all along the colon and over the appendix; anemia. (Figures 14 and 15 after 12 hours of barium ingestion and also with opaque enema.) Normal gall bladder with a stone. Evacuation of barium at 18 hours. Note the irregular picture of cecum, ascending and transverse colon, with small "saw-toothed" contours, with noticeable deformities of cecum and the presence of very small quantities of barium in left part of transverse colon. Also notice aspect of descending colon and its "saw-toothed" contour at its inferior half. Amebic cysts, ankylostoma, trichocephalus, and *Ascaris* eggs in stool. Greatly improved during last year with anti-amebic and parasiticide treatment.

Case 8741. Six gall-bladder colics. Dysenteric antecedents 12 years before. Negative coprologic examination. Gall bladder not visible after oral cholecystography. Bile examination after duodenal intubation showed cholecystitis without stones. (Figures 16 and 17, the first one taken at six hours after barium ingestion and the second one 24 hours later and also with opaque enema.) Notice cecal deformations due to post-operative adhesions. There was gastric retention after six hours; owing to the ingestion there was narrowing of transverse colon, hypersegmentation and "saw-toothed" contour of its middle third, and after enema there was appreciable distention of transverse colon with persistence of hypersegmentation at its lower edge. Medical treatment for cholecystitis and colitis with little improvement after four months.

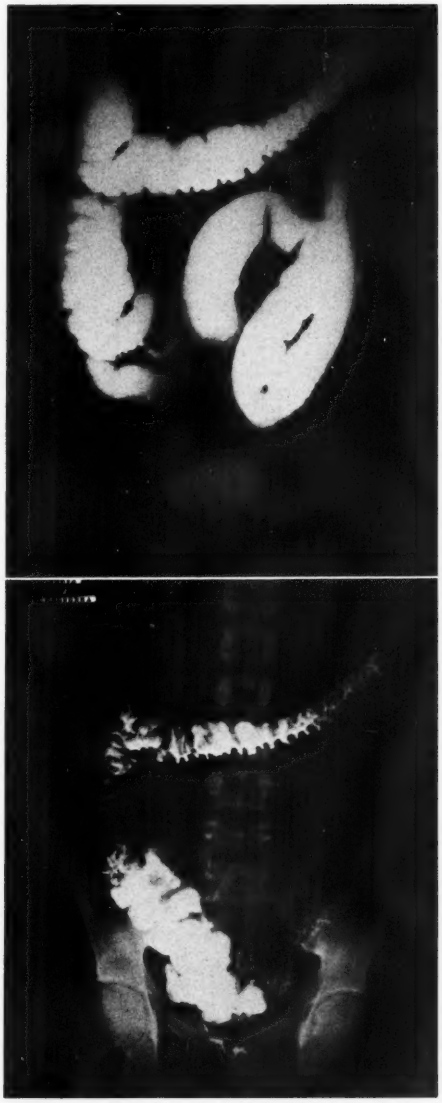

Fig. 20 (*above*). Fig. 21 (*below*).

Case 8704. Clinical and roentgenologic diagnosis of chronic appendicitis, confirmed by operation. There were found membranes on cecum and ascending colon and an obviously inflammatory process of appendix. Patient was well for six months after which time he had strong pain along the cecum and right colon. Figure 18 (roentgenogram made before operation) showed signs of colitis, and although there were no dysenteric antecedents nor amebic cysts in the stools, he was submitted to treatment and has improved. Gall bladder was normal.

Cases 6020 and 10082. The first examination, shown in Figures 19 and 19-*A*, was made in September, 1932, by barium ingestion, and Figures 20 and 21, taken

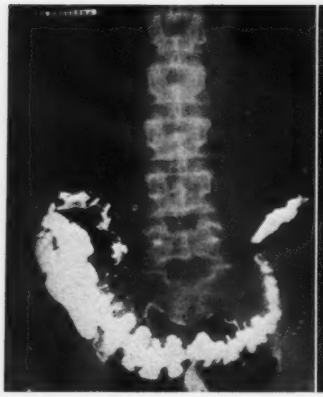

Fig. 22.

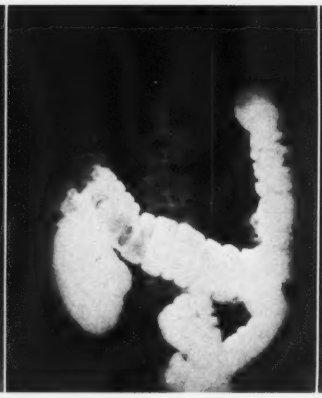

Fig. 23.

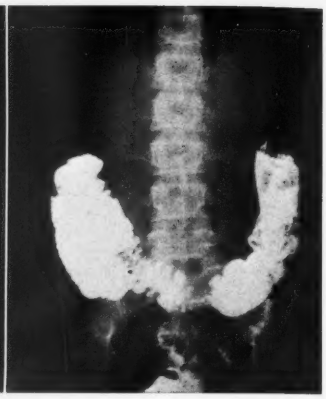

Fig. 24.

with "diagnotorine" enema and imbibition of mucosa, were made in October, 1936. Without dysenteric antecedents. Patient suffered from epigastric cramps, lasting for one or two hours. At first examination, attention was called to unequal hypersegmentation of colon with narrowing and small "saw-toothed" contours in some sites. Had a very incomplete antiamebic treatment until second examination. At this time the examination by ingestion gave identical results; with enema it showed narrowing and shortening of colon with numerous small segmentations; folds of mucosa were quite normal in descending colon and abnormal impregnation of rectum and terminal part of sigmoid was confirmed. Proctoscopic examination showed small ulcerations in those sites. Amebic cysts in stools. Cramps disappeared with extended antiamebic treatment.

Fig. 23-*A*.

Case 10071. Very old dysenteric antecedents. No amebic cysts in stools, nor ulcerations at proctoscopic examination. Improved with treatment. (Figures 22, 23, and 24 taken after ingestion as well as with "diagnotorine" enema and mucosa impregnation.) Notice ptosis of transverse colon, dilatation of cecum and of transverse colon with enema; unequal hypersegmentation without dilatation of transverse colon by ingestion, and the small "saw-toothed" contours of descending colon and cecum. (See also Fig. 23-*A*.)

*First Experimental Case, San Juan de Dios Hospital* (*M. J. H.*).—Acute dysentery with amebic cysts in stools. Very ulcerated mucosa and pseudo-membranes at proctoscopic examination. It was only

Fig. 25.

Fig. 26.

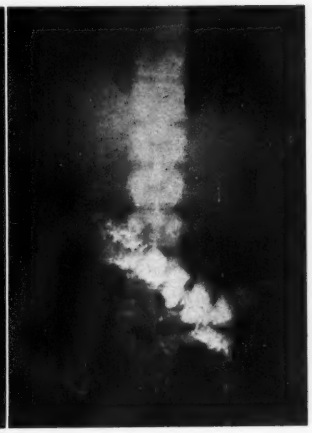

Fig. 27.

possible to reach the long sigmoid with the "diagnotorine" enema. See Figures 25 and 25-*A*, from which will be clearly appreciated the small extensibility of walls of intestinal segment examined, hypertrophy of mucosa folds, and "saw-toothed" contours, especially noticeable at terminal part of sigmoid.

*Fourth Experimental Case* (*R. B.*).—Dysentery just after acute period. Clinical signs of hepatic abscess. Isolated round ulcerations covered with a gray coating and located preferentially on rectum valves. Congested mucosa around ulcerations. Numerous amebic cysts in stools. The rectal segment most affected is seen with opaque enema (Fig. 26), rather dilated with gases, without other peculiar radiologic appearance. Sigmoid contours are regular except at its terminal part where they become "saw-toothed." Flattening of right flexure of colon due to compression by liver. In Figure 27 is shown the abnormal impregnation of mucosa at terminal part of sigmoid.

*Fifth Experimental Case* (*J. C.*).—Acute dysentery. Numerous *E. histolytica* cysts. Numerous bleeding ulcerations at rectal region with mucosal edema around them. Figure 28, taken with opaque enema, does not show anything special at rectum. Notice aspect of transverse colon and part of descending colon, where the appearance is that common to all ulcerative colitis.

*Sixth Experimental Case* (*S. A.*).—Note Figure 29 (with "diagnotorine" enema) and Figures 30 and 30-*A* after a stool. Amebic cysts in the stool: bloodless diarrhea. No ulcerations observed at proctoscopic examination. Notice contours of terminal portion of sigmoid in both views, as well as mucosal impregnation of that intestinal segment seen in second view.

Fig. 25-*A*.

Fig. 28.

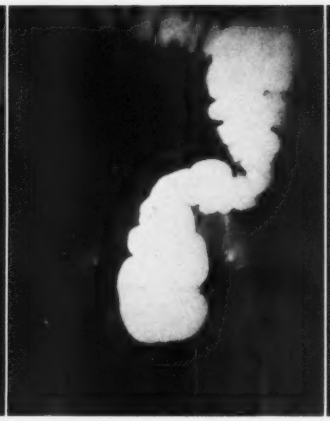

Fig. 29.

Fig. 30.

*Seventh Experimental Case* (*A. S.*).—Acute dysentery; numerous amebic cysts. Proctoscopic examination showed sound mucosa at end of sigmoid and deep bleeding ulcerations at rectum as well as pseudomembranes and mucosal edema at anterior wall of rectum. In Figure 31, taken with opaque enema, no irregularities of contour are observed at rectum; gaseous dilatation at its top part. Wall induration, as well as narrowing and "saw-toothed" contours at the sigmoid zone near the middle line are observed (Fig. 31-*A*).

*Eighth Experimental Case* (*S. A.*).—*E. histolytica* cysts, no digestive phenomena and normal proctoscopic aspect. In Figure 32 are clearly seen "saw-toothed" contours and narrowing of descending colon at union

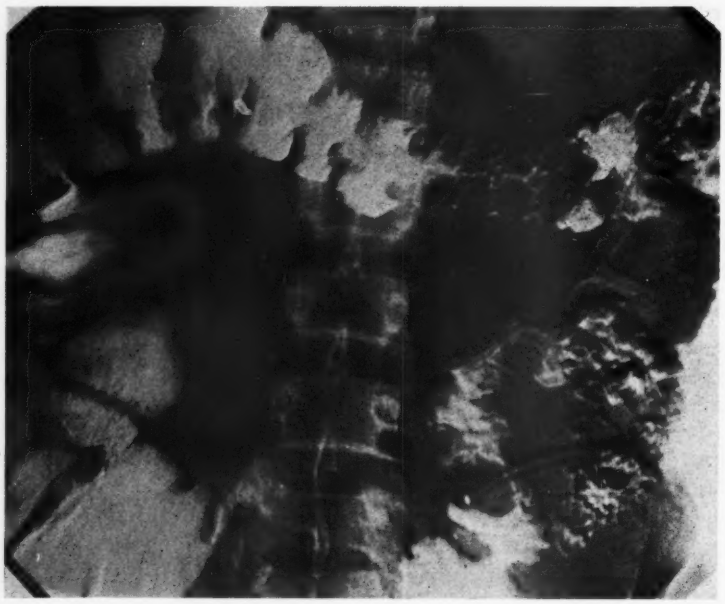

Fig. 30-*A*.

Fig. 31.

Fig. 32.

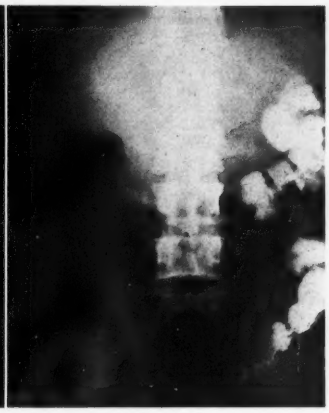

Fig. 33.

of middle third with superior third. Figure 32-*A* shows flattening of right colon flexure due to compression by liver.

*Ninth Experimental Case* (*P. E.*).—Acute dysentery; amebic cysts; numerous ulcerations seen at proctoscopic examination. In Figure 33 is noticeable only the small extensibility of left terminal part of colon and an abnormal mucosal impregnation of rectum at ulceration and edema sites.

*Thirteenth Experimental Case* (*A. F.*).—Recurrent dysentery; amebic cysts; sigmoid and rectum ulcerations (Fig. 34, with opaque enema). Notice regularity of rectum and of beginning of sigmoid, and great length of the latter. Slight "saw-toothed" contours of part of sigmoid. In Figure 35—by ingestion—barium meal is seen at stomach below transverse colon. Notice "saw-toothed" contours, narrowing and unequal segmentation of that sigmoid segment below the transverse colon.

*Fifteenth Experimental Case* (*L. C.*).—Dysenteric phenomena; only *B. coli* cysts

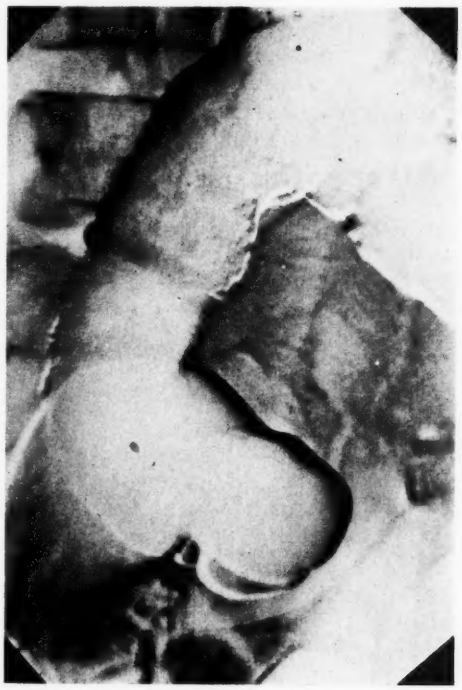

Fig. 31-*A*.

Fig. 32-*A*.

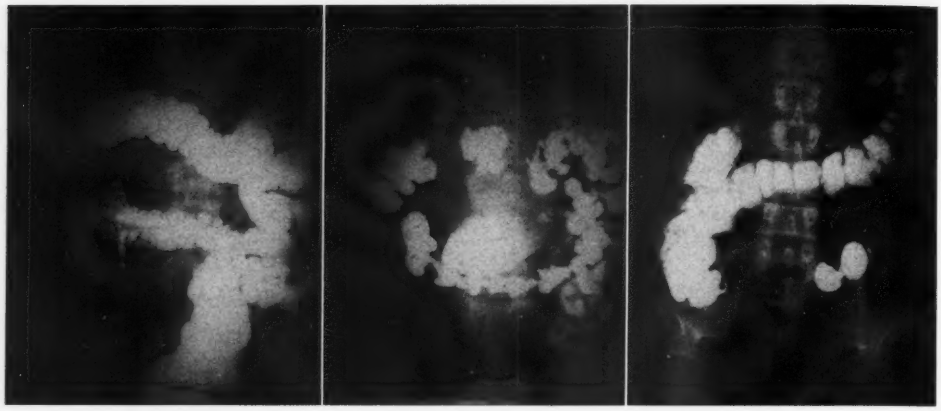

Fig. 34. Fig. 35. Fig. 36.

found; normal mucosa seen at proctoscopic examination (Fig. 36, with opaque enema). Note the difference of aspect as compared with other cases. In Figure 37 we observe mucosal impregnation while aerocolia is present.

*Seventeenth Experimental Case* (*R. A.*).—Dysentery after acute stage; ulcerations shown by proctoscopic examination. In roentgenographic film (Fig. 38, with opaque enema) one can observe only a very long and hypersegmented sigmoid. Note in Figure 39 impregnation of mucosa at terminal part of ulcerated bowel.

## SUMMARY AND CONCLUSIONS

1. *Endamœba histolytica* amebiasis is very frequent in the whole territory of the Republic of Colombia. Such frequency is less in cold climates at high altitudes, like Bogotá, the capital of the Republic. However, the extension of amebiasis among the inhabitants of Bogotá is demonstrated, among other things, by the fact that in 6,540 coprologic examinations carried out at various laboratories in town, there were found 1,319 cases with *Endamœba histolytica*—that is, 20.16 per cent of the patients examined.

2. Although Colombian physicians and microscopists have a good practice in the diagnosis of amebiasis, the variableness of the clinical aspects of the disease and the lack of confidence in isolated laboratory examinations explain why many cases may pass by unnoticed.

3. Chronic amebiasis patients without dysenteric phenomena and with an exceedingly variable symptomatology form a group of patients difficult to diagnose clinically and in whose examination x-rays are most useful. Neither acute amebic patients nor those with recurrent dysenteric attacks pass unnoticed by the clinic physician and for that reason such patients are seldom sent in for a radiologic examination. As regards carriers of germs, without clinical symptoms, their radiological examination is necessarily exceptional.

4. In 5,067 patients radiologically examined since 1931, a diagnosis of amebiasis has been made in 4 per cent, afterward confirmed, among those suffering from digestive troubles. The symptomatology of these patients was quite variable and none of them had any colitis signs when examined.

5. By means of a complete radiologic examination of the digestive tract, I several times found some signs that allowed me afterward to confirm the original amebiasis diagnosis.

6. Experimentation on 25 patients with radiologic, proctoscopic, and laboratory studies allowed me to observe in amebic patients with dysenteric phenomena in acute stage or soon after this, findings

identical to those from chronic amebiasis patients.

7. There is very little scientific literature available on amebiasis, taking into account that such disease is so frequent in tropical countries and that x-rays may be very useful for its diagnosis.

8. I often found an appreciable gastric retention in amebic patients, at the end of six hours. In some patients suffering from gall-bladder colics, clinically determined, the gall bladder was not visible by Graham-Cole's method, the examination of bile was normal, and colics disappeared with the anti-amebic treatment. Very often I found the liver volume increased and causing a deformation of the colon right-angle, and in the duodenum and ileum I could not find any peculiarity.

9. Generally the cecum-colon transit was accelerated during the first few hours but later on it was common to observe a retarded intestinal evacuation.

10. One of the most important points observed in the studies made by barium ingestion was the increased number of haustral markings of the colon, especially in the transverse colon, with variable frequency and intensity, and its corresponding narrowing.

11. In some cases there were, in the colon, unequal distribution of the barium meal, diminution or absence of haustral markings, atony of colon walls, and aerocolia.

12. The group of radiologic findings most frequently found was formed by a segmentary induration of the cecum or colon walls and the presence of "saw-tooth" contours. Such a radiologic aspect or picture, located at isolated intestinal segments, is characteristic of the presence of ulcerations in those sites.

13. The study of mucosa by impregnation does not seem of any practical utility in amebiasis diagnosis.

14. Generally the same radiologic data of chronic cases were observed in acute amebiasis, although not in cases at the beginning stage.

15. The descending colon, the colon segments adjacent to the hepatic and splenic flexures, the sigmoid, and lastly the other colon segments are the sites radiologically indicated where the disease is located. As a rule, the lesions of the rectum, without impregnation of the mucosa, pass unnoticed in the examinations by ingestion and enema.

Fig. 37 (*above*). Fig. 38 (*below*).

16. The above observations, made in chronic amebiasis patients and in those

experimentally studied, corroborate the aforesaid conclusions.

*It is my opinion that the complete radiologic investigation of the digestive tract, carried out in patients in the city of Bogotá when the above-described radiologic signs are found, allows the physician to focus his study on amebiasis. He thus obtains a valuable help in the diagnosis and treatment of that disease.*

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# ROENTGEN AND LIGHT THERAPY OF INTESTINAL AND PERITONEAL TUBERCULOSIS[1]

*By* EDGAR MAYER, M.D., *and* MARTIN DWORKIN, M.D., *New York City*

ROENTGEN and light irradiation have been applied to intestinal and peritoneal tuberculosis with results sufficiently favorable to warrant their more frequent trial. In this paper will be discussed briefly their effects on animal and human tissue, the indications and technic of usage in accord with the pathology, the clinical applications, and comparative clinical results.

*Effects of X-ray on Body Tissue.*—The susceptibility of cells to x-ray varies according to a specific range of sensitiveness of each histologic variety. Certain kinds are injured or destroyed by small doses of x-ray, while others resist and tolerate large doses. With excessive dosage even the least radiosensitive varieties of cells may be injured or destroyed.

Cells most radiosensitive (1) are: lymphoid cells or lymphocytes, present in spleen, lymph nodes, intestinal lymph follicles, circulating blood, bone marrow, thymus, tonsil, etc.; polymorphonuclear leukocytes and eosinophiles in blood or tissues; epithelial cells; endothelial cells of blood vessels, pleura, and peritoneum; and connective tissue; muscle, bone, fat, and nerve cells.

The most susceptible cells are those which, from a metabolic standpoint, are younger and mitotically more active; the cell age is less important than the specific vulnerability of different cell varieties, in determining reaction to x-ray exposure.

*Effect of X-ray Exposure on Intra-abdominal Lymph Glands.*—Lymphoid tissue in the intestinal wall and in intra-abdominal and mesenteric glands responds biologically to x-ray irradiation in the same manner as lymphoid cells elsewhere in the body. Exposure of the entire animal body shows that, depending on the degree of dosage and the interval between their irradiation and death, there is marked destruction of lymphocytes. Lymphocytic disintegration may take place within 15 minutes after exposure. As lymphoid follicles disappear stroma becomes more prominent. The lymph glands atrophy and are progressively reduced in volume. Phagocytic reticular cells ingest nuclear chromatin of destroyed cells which finally undergoes intracellular digestion. Some regeneration of lymphoid tissue occurs after from seven days to three weeks.

*Effect of excessive radiation on intestinal mucous membrane* varies for different parts, the mucosa of the small intestine being more sensitive than that of the colonic mucosa. The duodenal and jejunal mucosa are the most sensitive portions of the alimentary tract and may be irritated with x-ray dosage insufficient to produce erythema of overlying skin. Within a few hours after a therapeutic dose is given to the upper half of the abdomen, digestive disturbances characterized by anorexia, nausea, and vomiting may occur, and after several days, diarrhea.

Warren and Whipple (2) have shown in experimental work that the mucosa of the small intestine is highly susceptible to hard and short wave roentgen rays and that an overdose may produce intestinal ulceration.

In animals exposed to excessive doses there is mucinous degeneration of intestinal epithelium, hyperemia, and edema of the mucosa and submucosa, and there may be desquamation of epithelium. If the reaction is not too severe, the mucosal defect may be repaired by epithelial regeneration or connective tissue replacement.

*X-ray Therapy of Tuberculous Lesions.*—The dosage for chronic inflammatory lesions, as tuberculous intestinal and peritoneal disease, must be larger than that

[1] Presented before the Fifth International Congress of Radiology, Chicago, Sept. 13–17, 1937.

used for acute inflammatory lesions. The most effective dose varies between 50 and 80 per cent of the limit of tolerance of the skin. In the skilled hands of an experienced radiologist, possessing modern equipment, capable of administering accurate dosage, deleterious effects upon the skin such as epithelial hyperplasia and malignant transformation due to chronic irritation, may be avoided. Dosage distinctly smaller than the maximal dose required in the treatment of tumors is recommended. For cure or maximal benefit it is important that irradiation be repeated a number of times at from three- to four-week intervals. Smaller doses may be repeated at shorter intervals. With repeated periodic exposure of the affected region, combined with exposure of the whole body to gradually increasing doses of ultra-violet rays, slow but complete resolution of the chronic inflammatory process may be obtained.

*Mode of action* of radiotherapy on chronic tuberculous lesions depends on two factors, the degree of leukocytic infiltration and the proportion of connective tissue and of degenerative products such as caseation and calcium. These factors govern also the time required to bring the lesions under control.

The rays do not exert a direct bactericidal action. Theoretically, the deleterious effects on the tubercle bacilli are brought about by a change in soil or body tissue. The organisms are believed by some to be destroyed by autolytic enzymes released from dying cells. It seems likely that destruction of infiltrating leukocytes liberates the antibodies and other protective substances within the cells, making these substances available for defense purposes. Perhaps the roentgen ray excites the epithelioid cells in their phagocytic action on the tubercle bacillus or possibly it produces a general effect through autotuberculinization. Of interest is the theory that defense substances of the reticulo-endothelial system contained in skin are sent into the circulation to make healing permanent.

In the application of heliotherapy and roentgen irradiation to intestinal and peritoneal tuberculosis, the nature of the pathology in the intestine and peritoneum (exudative or proliferative) must be defined and correlated with that of the pulmonary tuberculosis, if the latter exists, before therapy can be offered.

*Ulcerative intestinal tuberculosis* is found in from 50 to 80 per cent of autopsies on persons dying of pulmonary tuberculosis. This establishes intestinal tuberculosis as the most frequent complication of phthisis.

Bacmeister, in 1921, was among the first to use x-ray therapy for this disease with favorable result. At Trudeau Sanatorium (3) the therapy was used alone and in combination with ultra-violet light, often with most gratifying results. The average dosage given in roentgenologic treatment over the abdomen was 5 milliampere-minutes (90 kilovolts, 2.5 to 3 milliamperes, filtered through 3 mm. of aluminum, tube distance 35 cm.). The authors found the "intestines very susceptible to roentgen rays and that reactions of some intensity with recurrence or increase of all intestinal symptoms could easily be brought about."

In the technic employed by Rother (4), an individual dose never exceeding one-third of a skin dose (200 r) is given over an area of the abdomen from 10 to 15 cm. in size through a compression tube at a distance of 30 cm., through a filter of 0.5 mm. of zinc or copper at a tension of 180 kv. Weekly or greater interval exposures are recommended, until each area has had an exposure of 600 r.

In many cases, roentgen-ray treatment has been combined with ultra-violet therapy, in cases in which light radiation alone did not give the desired results. However, caution is advised, in combining the therapy, against the danger of a burn from an otherwise safe dose of roentgen rays and also against the possible cumulative effect of roentgen rays. An overdose may produce intestinal ulceration, and deaths have been reported from severe intoxication following roentgen-ray treatment, due to ulcerative enteritis. It is generally agreed that great caution is required in treating the ulcerative tuberculous intestine char-

acterized by caseation. In cases in which it is characterized by granulation tissue, that is, tending toward the proliferative or hyperplastic, as apart from the exudative or caseating form, it is believed the roentgen rays can cause general regression and fibrous transformation. In cases tending toward caseation, x-rays may precipitate breakdown.

*Peritoneal tuberculosis* is usually secondary to and takes place by direct extension from a tuberculous lesion in the intestine, caseating abdominal retroperitoneal or pelvic lymph glands or organs in the pelvis. It may also occur by metastasis from a remote primary focus in the lung or cervical lymph glands. Postmortem records show the lung involved in over 90 per cent of cases.

In treating this form of tuberculosis x-rays were first successfully used in 1899 by Bircher, Ausset, and Bedard. Since that time much has been reported in medical literature. Great benefit apparently can be obtained from x-ray irradiation of this condition. Results are not so favorable when there is serious co-existing involvement of the lungs or other regions.

In the *fresh ascitic or exudative* form, particularly good results have been obtained with x-ray therapy. The *plastic type with extensive adhesions and omental tumors* is not easily influenced, although ultimately great benefit has often been obtained in these cases also. In the *caseous type* results are not so good despite treatment contained over a long period.

In the presence of abdominal distention, ascitic fluid is first drained from the peritoneal cavity and the abdomen then irradiated (5). Both low voltage x-rays with aluminum and high voltage rays with copper filtration have given good results. Our technic, following that of Knox and Levitt (6), has been to map out the abdomen into four anterior and four posterior fields, a dose of from 10 to 15 per cent U.S.D. applied to one anterior and one posterior field once weekly, at a target distance of from 30 to 50 cm. This treatment is continued for six months. Temperature elevation over one degree following treatment indicates decrease of dosage. In cases in which the affected region was entirely below the umbilicus, a dose of 20 per cent U.S.D. was administered once weekly over anterior and sacral fields of sufficient size to include the lesion. In cases in which the upper abdomen was involved, the dosage was reduced. In the caseous types, the dosage applied was smaller than the above.

In the exudative form remarkable improvement can be obtained. Immediately after exposure there can be great relief of abdominal pain, shrinkage of the abdomen, drop in temperature, and disappearance of ascites. The general condition improves, appetite returns, and the patient gains weight. In some cases in which treatment was begun early, the patient became afebrile in three days, and ascites disappeared in about ten days.

The average technic to be employed is: frontal and posterior exposure with 180 kv., 6 ma., 1 mm. copper filter, 40 cm. distance, giving 200 r surface doses per field (one-third skin dose) once weekly for two months. This course may be repeated in three months. To help the roentgen effect, one may also employ heliotherapy in the form of natural or artificial sunlight.

Caution should be observed, in irradiation of the abdomen, to avoid injury to spleen and internal genitalia by overdosage. These organs are highly sensitive to x-rays. Because of scattered secondary radiation, no protection is afforded by covering these parts.

*Heliotherapy for Intestinal and Peritoneal Tuberculosis.*—Light therapy, both natural and artificial, is of definite value in the treatment of intestinal and peritoneal tuberculosis. Used alone or in combination with roentgen irradiation, it has at times proven an important adjuvant to rest and general hygienic therapy in selected cases. There is still considerable difference of opinion as to which regions of the light spectrum are most efficacious, as well as confusion as to which pathologic types of intestinal and peritoneal disease respond best. Natural heliotherapists, especially

those working in high altitudes, emphasize solar radiation and ærotherapy. On the other hand, those working in low lands and cloudy climates have stressed the use of artificial lights.

The rôle of ultra-violet energy has been established through animal and human studies. The exact part played in the clinical usage of light by the total visible spectrum is difficult to say, although in all probability it is in some way physiologically effective.

The additional part played by the action of moving air on the skin in the solar treatment of extra-pulmonary tuberculosis must not be discredited. Probably the combination of all factors contributes to the end-result.

In the choice of an artificial source of light, a sufficient quantity of radiation must be present.

For therapeutic purposes the sun, the mercury vapor arc in quartz, and the flaming carbon arc burning cored carbons filled with mixtures of carbon dust and metals have been the chief ones of practical importance. The mercury vapor lamp has been particularly developed for its emission of ultra-violet, although it emits also well in the visible part of the spectrum. A carbon arc consuming 25 amperes or more and burning specific carbons, such as "sunshine" carbons, closely approximates highland sunshine. Carbon arcs of varying amperage and with special cored carbons will emit, almost according to the needs, widely varying intensities in many regions of the light spectrum.

The erythemal reaction is really the only physiologic one that is established with a relatively high degree of accuracy. As a criterion it is a simple and practical means of preventing severe burns, and as a reaction it is a good means of judging the effectiveness of a lamp.

Exact clinical indications for different sources of light have not yet been defined. For intestinal and peritoneal tuberculosis both artificial sources of light have shown great value (7).

*Secondary Intestinal Tuberculosis.*—In an active febrile pulmonary tuberculosis complicated by active intestinal tuberculosis, *mercury quartz irradiations* have been regularly used by many for the intestinal complication and not infrequently with favorable effect. In such cases the activity and nature of the pulmonary disease have been disregarded. The unfavorable empirical results obtained when other treatments have been used justify this as an indicated therapy.

Artificial light and solar therapy, as well as a rich vitamin diet, should be used in most cases, as they frequently relieve the symptoms and bring about recovery.

Excellent results are obtained with the use of artificial sources of radiation, with general exposures either of the mercury arc in quartz or carbon arc sources. The results depend on factors such as the general status of the patient and extent and nature of the disease in the intestine. Those with far advanced pulmonary and intestinal tuberculosis with little remaining resistance cannot be expected to respond, but intestinal tuberculosis to-day is healed in many patients, and often autopsies have confirmed this.

With light exposures and hygienic treatment, the symptoms referable to the intestinal tract generally vanish during the first few months of irradiation, but the exposures should be continued for at least six months to two years. The loss of symptoms is frequently surprising, abdominal pain and discomfort disappearing, diarrhea and fever subsiding quickly, and general improvement taking place. Roentgenologic studies show that the intestinal irritability as visualized by x-ray defect clears up entirely in many instances. It is usually best to continue light therapy for many months after an apparent cure has occurred.

Patients who do not respond to light should be given roentgen treatment. General body exposures to light, combined with local roentgen irradiations in suitable doses, often yield results superior to those obtained with either one or the other.

*Peritoneal tuberculosis treated by heliotherapy* over many months, as an adjunct to rest and hygienic measures, is often markedly improved, with lessening of symptoms and local signs. When the peritoneal lesion has become quiescent, it is often possible to effect surgical removal of the primary focus, such as tube or appendix, and then, with a few more months of treatment, bring about healing of the peritoneal process.

In peritoneal tuberculosis, light therapy always deserves a trial first. The *serous exudative* type generally responds to light irradiation, both in children and in adults. The *dry proliferative form*, usually adhesive, is more refractory yet often responsive. When there have been ulcerations and large *caseous* lymph nodes, as commonly seen in children, the results are most unsatisfactory. When the disease is of long standing, healing is more difficult than when irradiation is begun a short time after onset.

Pain under light therapy usually disappears rapidly, especially in children. Large quantities of ascitic fluid may disappear in a few months. To cite examples:

Case 1 represents an unusual one of peritoneal tuberculosis. Mr. C. H. (patient of ours and of Dr. A. Hyman), in June, 1935, complained of swelling of right side of abdomen and pain in both inguinal regions, loss of weight, slight fever, nausea, and anorexia. There was a firm discrete orange-sized tumor mass in the right lumbar gutter, extending from a few inches above the umbilicus to the pelvis. There were also a few small scattered similar masses in the abdomen. History was given of pleurisy with effusion, 20 years previously. The lungs were clear. An erroneous diagnosis of retroperitoneal lymphosarcoma was made by three consulting physicians.

Sixteen treatments of roentgen irradiation of tumor dosage were given over a period of 40 days by Dr. W. Harris, of Mt. Sinai X-ray Department. The factors used were as follows: 180 kv., 0.5 mm. copper, 1 mm. aluminum filter; 46 cm. distance, size of portal 20 × 24 cm. The right side of the abdomen was cross-fired through the anterior and posterior portals, 200 r being given at each treatment. The anterior field received 1,750 r measured in air, 1,350 r being given to the right lumbar region, a total of 3,700 r. Under this intensive therapy the masses dwindled gradually in size but persistent fever, 101° to 102° F., developed. Laparotomy was performed and a quart of thick yellow pus aspirated from the liquefied tuberculous caseating peritoneal mass. The patient made an uneventful recovery and has remained clinically well.

Although the usual dosage recommended for treatment of peritoneal tuberculosis, as previously stated, is distinctly smaller than that required in the treatment of tumors, nevertheless, it may be, in the light of our experience with this case, that larger dosage is required for deep-seated infections than we have been giving them in the past. In this case the patient was treated on the basis that we were dealing with a neoplasm.

Case 2 is one of hypertrophic intestinal tuberculosis. This patient has been under medical care for the past three years, complaining of abdominal distress after meals, with sour eructation, dull ache in the right lower abdomen, irregular bowel movement, loss of weight and strength, and a chronic slightly productive cough. On examination a mass was felt in the right lower quadrant, suggesting ileocecal hypertrophic tuberculosis.

X-ray chest films showed proliferative tuberculous lesions in both upper lobes, more extensive in the right upper third; moderate leukocytosis and a slightly active sedimentation rate were found. Sputum and stool examinations, at this time, were negative for tubercle bacilli.

Re-examination of bowel after barium enema showed narrowing and irregularity of cecum and part of ascending colon, terminal ileum being also involved. Findings were suggestive of granuloma involving cecum and part of ascending colon and also terminal ileum. A diagnosis of hy-

Fig. 1. Case 2. Narrowing and irregularity of the cecum, terminal ileum, and ascending colon.

pertrophic intestinal tuberculosis was made.

Light therapy to the abdomen was carried out with daily mercury vapor quartz lamp irradiations and natural sunlight in tanning dosage. The patient improved clinically. However, the ileocecal mass persisted and there were still abdominal complaints with occasional nausea and semi-solid stool. Therefore, x-ray therapy was applied—cross-firing radiation to the anterior and posterior right abdomen, giving 200 roentgen units at each treatment for four weekly exposures. The factors employed were similar to those used in the first case: 180 kv., 0.5 mm. copper, 1 mm. aluminum filter; 46 cm. distance.

Twelve weeks following this therapy the mass was no longer palpable. The filling defect by x-ray has markedly diminished. The patient has gained 37 pounds and has remained clinically well for the past seven months.

Fig. 2. Case 2. After therapy lesion is less extensive, cecum fills better.

## CONCLUSIONS

1. The use of roentgen-ray and light radiation for treatment of intestinal and peritoneal tuberculosis is often productive of good results, warranting more general use of these measures as adjuvants to rest and hygienic treatment.

2. A trial of tumor dosage of x-ray under careful watching is indicated in proliferative forms of intestinal and peritoneal tuberculosis that have not responded to smaller doses.

3. With x-ray treatment, best results are obtained in hyperplastic and simple proliferative forms of intestinal and peritoneal tuberculosis, and especially when applied early in ascitic forms of peritoneal tuberculosis.

4. With light therapy, both natural and artificial, the ascitic and proliferative forms of peritoneal tuberculosis as well as the proliferative and ulcerative forms of intestinal tuberculosis are generally responsive in patients not too critically ill.

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# LOCAL AND GENERAL IRRADIATION IN HODGKIN'S DISEASE[1]

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IRRADIATION remains the chief resource in the treatment of Hodgkin's disease. Surgery is worth considering only in the earliest stages of those rare cases in which the apparent first focus of the disease is limited to an accessible group of lymph nodes. Even in such cases, early additional treatment of the affected zone and contiguous lymph node areas by irradiation seems imperative.

All the attempts to prove various theories of the cause of Hodgkin's disease and to devise, based on those theories, more or less specific methods of constitutional treatment, have failed to produce results sufficiently impressive to lead to abandonment of radiation therapy. That fact stands as the best proof of the actual lack of general value of any of these proposed constitutional methods.

However, the search for etiology and a possible specific constitutional remedy should be pursued, for there is much about Hodgkin's disease that forbids its classification strictly as a tumor process, and that indicates that it begins, at least, as an inflammatory disease. From a clinical standpoint the fever, the rashes, the eosinophilia, the local and general distribution and modes of extension of infiltrations, the frequent traces of allergic phenomena, the common polynuclear leukocytosis, all point to an inflammatory rather than a truly neoplastic nature.

Yet, until something better is found we must do our best with the proven palliative agent, radiation.

Accepting, then, radiation as the present best available agent for the treatment of Hodgkin's disease, we may next inquire whether there is any preference as to the technic of irradiation.

It is extremely difficult to draw conclusions concerning the merits of various technics, either from a study of reported series of cases or from a review of one's own material. The difficulty of drawing conclusions is due to (1) wide variations in recommendations made by different authors, when they attempt to lay down general rules; (2) necessary wide variations of technic in any series of cases, or even in one case, because of the great diversity in types of lesions. In a disease so variable, statistics of length of survival in small series of cases mean but little, and in a disease in which no stable technic of treatment can readily be developed it is next to impossible to draw valid conclusions even from a large series of cases.

Some have attempted to distinguish between cases treated "according to plan"—that is, cases in which full co-operation of the patient was received, and all the treatment was given in the way in which the clinician intended it should be given, and cases not so treated, and to report their results on the cases supposedly ideally treated. Under practical conditions it would seem very difficult to say that very many cases could be treated just as one would wish.

Looking back to fifteen or seventeen years ago and comparing methods of irradiation of Hodgkin's disease then with current methods, one can trace a considerable evolution. In the early 1920's x-ray treatment of Hodgkin's disease was almost exclusively by low voltage x-rays, directed to the more obvious seats of disease, that is, to external masses of nodes, to mediastinal masses, and to the spleen. It was customary to give to each area to be treated single erythema or suberythema doses of low voltage x-rays (100 to 135 kv., 25 to 30 cm. T.S.D., 3 to 4 mm. Al filtration).

[1] Presented before the Fifth International Congress of Radiology, at Chicago, Sept. 13–17, 1937.

Results, as far as these more readily discernible foci were concerned, were approximately the same as now; that is, being in the main a radiosensitive disease, it responded usually with good regression of these evident foci. However, little was done for the more advanced cases with their deeper foci, of which in those days we were often not aware until autopsy was done.

Toward the latter part of the 1920's the increased availability of high voltage x-rays led to increased use of this more penetrating agent. At the same time, we were beginning to pay more attention to foci of disease which theretofore had been rather neglected. That is, we were more alert to irradiate the mediastinum and retroperitoneal region, and to follow some plan of irradiation of lymph node areas that were reasonably certain to be involved, even though no gross foci could be demonstrated in them. For example, if a packet of diseased nodes was found at the base of the neck and also in the axilla, we began to favor irradiation of the mediastinum and possibly of the upper retroperitoneal region even in the absence of demonstrable disease in those areas. We did so because experience at the autopsy table and reflection upon the apparent source and mode of extension of the disease led us to believe that Hodgkin's disease actually arises commonly in internal foci, and that if we confined our treatment to irradiation of the masses in the neck and in the axilla we would be treating only the superficial manifestations of the process. At this period treatments usually were of the order of 500 to 700 r of high voltage x-rays (185 to 200 kv., 30 to 50 cm. T.S.D., and 0.5 mm. Cu filtration). However, we never pursued a plan of systematic local irradiation of all lymph node areas, including those not even presumably involved.

The next step in the late 1920's and early 1930's was that we began to pay more attention to a search for more obscure foci. We began to suspect and find nasopharyngeal, pulmonary, gastro-intestinal, and other visceral foci, and lesions of the bones. Then, about this time, the wave of enthusiasm for the divided dose technic led to increasing experiments with smaller and repeated doses to each area. In general, the divided dose method seems to be the prevailing one in most centers to-day. While there are, of course, wide variations in the mode of application of divided doses, the general tendency in recent years has been to use not much over 200 r of high voltage x-rays to one area at a time—frequently considerably less—and to give additional fractional doses at various intervals, depending on the individual indications, until a comparatively large total dose has been given, in the order of anywhere from 1,200 to 2,000 r or more to each field.

Such a method of treating Hodgkin's disease may work very well, particularly in clinics where there is time and space to permit a great deal of individual attention to each patient. However, it has serious disadvantages, particularly in cases that have many areas to be treated. The large total amount of body dose received by such patients frequently results in a considerable depletion of strength and depression of hematopoietic function. The frequent trips which ambulatory patients must make to the clinic in order to complete a protracted series of treatments contribute to their exhaustion.

Looking back, again, to the cases treated before we began to fractionate our doses to the present degree, we gain a growing impression that with fewer and larger doses they fared with much less exertion, they obtained good regressions, they seemed to suffer from anemia and leukopenia less commonly than the later cases, and some of them are now among the longest survivors. Of course, in forming such a judgment we must be mindful of the fact that the cases treated by divided doses are more recent, and that not enough time has yet elapsed to enable us to say whether they will show as good a survival rate. However, we are rather definitely forming the impression that, in general, it may be advantageous to return whenever possible to treatment by a smaller number of doses

per field, using larger single doses, of the order of 400 to 600 r.

The question of the choice between 140 kv. x-rays and 200 kv. x-rays, like most other questions as to choice of technic in the treatment of a variable disease like Hodgkin's disease, cannot well be settled by statistics, but rests on impressions gained by experience. Regression of superficial nodes can no doubt be brought about satisfactorily by low voltage x-rays, but it seems to me that 200 kv. x-rays offer enough advantage in added depth dose—and in the corollary, relative sparing of damage to skin and subcutaneous tissue—to call for their use in most of the lesions except the most superficial ones. Certainly for deep-seated lesions there appears to be little justification for the idea of using 140 kv. x-rays routinely, and saving high voltage for use in the later, more refractory stages. It would seem to be much preferable to treat deeply situated lesions by high voltage x-rays from the beginning.

The foregoing brief summary of evolution of methods of local irradiation for Hodgkin's disease has brought us from the earlier simpler methods of irradiation of obvious masses of enlarged nodes and spleen to the later, much more complicated, attempts to treat all the foci of the disease.

It has rather tardily come to be recognized that the treatment of Hodgkin's disease is much more complex than the irradiation simply of certain lymph node areas. A survey of any considerable group of cases, closely followed, shows that practically any tissue or organ of the body may be directly or indirectly affected. Many types of involvement of nervous system, central or peripheral, destructive or productive lesions of bones, pleural and peritoneal effusions, lesions of gastro-intestinal and urinary tracts, bizarre dermatological lesions, are among the complications that may arise.

We have in our files from 1918 to December, 1935, 339 cases diagnosed as Hodgkin's disease. Of those cases, 220 have been considered, after careful review, as being satisfactorily proved by biopsy. It is of interest to note briefly the occurrence in this series of some complications or features of the disease which pose special problems for treatment (Table I).

TABLE I.—SOME COMPLICATIONS OF HODGKIN'S DISEASE, OCCURRING IN A SERIES OF 220 CASES VERIFIED BY BIOPSY

Admitted between Jan. 1, 1918, and Dec. 31, 1935

| | |
|---|---|
| Lesions of the lung | 29 per cent |
| Pleural effusion | 17 per cent |
| Ascites | 8 per cent |
| Jaundice | 6 per cent |
| Itching | 29 per cent |
| Various cutaneous lesions | 13 per cent |
| Herpes zoster | 4 per cent |
| Various neurological lesions | 12 per cent |
| Lesions of bones | 18 per cent |

No doubt all the percentages shown in Table I would be considerably increased if we had an opportunity to follow all cases to their termination. Those enumerated are merely some of the leading complications. To mention all the others which we have observed or which have been noted by others would make an extremely long list containing symptoms referable to all tissues and parts of the body.

Thus a full acquaintance with all the possibilities of Hodgkin's disease carries one into all domains of medicine and there is no specialist who may not at some time have to meet some feature of this disease as it affects his particular interest. Thus, this one type alone of the protean lymphomatous diseases may stand as an example of the necessity for the unity of medicine, an idea to which this Congress is dedicated.

The great diversity of lesions found in Hodgkin's disease will probably always inhibit the establishment of any routine of treatment, certainly at least of any routine method of irradiation. Irradiation for Hodgkin's disease will, no doubt, always have to be individualized. Yet, within the limits of individualized treatment, there is a rather wide latitude, permitting varied technics, any of which may secure good palliation. It is doubtful whether for any case as a whole we shall ever be in a position to say that so, and just so, should that

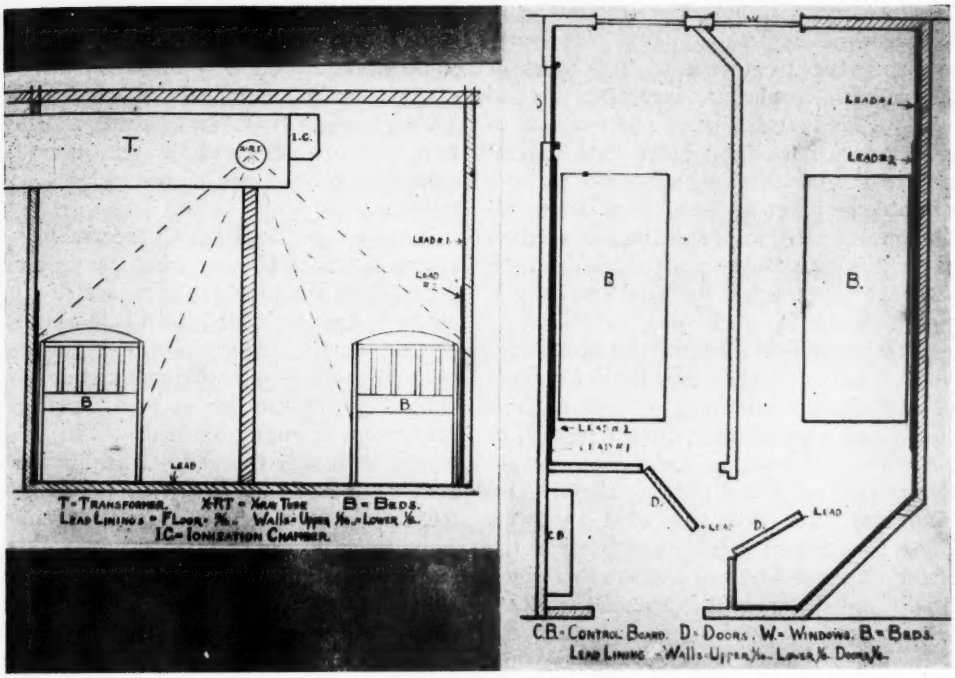


Fig. 1. Diagram of present Heublein unit for irradiation of the entire body.

case be treated. Such a routine may possibly be worked out for a given mass of nodes, but not for all the manifestations to which the case may become subject.

Various adjuvants to treatment are noteworthy. It is important for the patient with Hodgkin's disease to pursue a regimen as for tuberculosis. Rest, good diet, and sunshine are great aids in improving his condition. Transfusions, when he becomes anemic, may be of marked benefit, particularly by putting him into better condition to withstand further irradiation. Quite frequently transfusions produce alarming febrile reactions, despite great care in blood grouping and cross-matching. In some such instances, however, we have found the patient improved following such a reaction.

Irradiation of the entire body as a method of treatment of Hodgkin's disease as well as of the other lymphomatous diseases, has attracted considerable interest in certain centers in Europe and to some extent in America in the last decade. For the most part, the whole body has been irradiated intermittently, the dose per sitting usually not exceeding 25 or 30 r. At Memorial Hospital we have employed the Heublein method, whereby the patient remains in a room sometimes for several days at a time (Fig. 1), receiving radiation from a tube at a distance of from 7.3 to 3.4 meters (1). The factors are so adjusted that the intensity is of the order of 1 r per hour: each 24 hours the patient receives about 18 to 20 r. Our total dosage for Hodgkin's disease has varied from 38 to 300 r, and is usually 50 to 75 r.

Our experience with the Heublein method began six years ago, in May, 1931, when the first unit was established. It was used for two years, being abandoned in May, 1933, only for reasons of economy. With that unit, 44 cases of Hodgkin's disease were treated. Three cases were treated by that method alone before the unit was abandoned.

On the basis of the experience gained with that unit a report was read at the

First American Congress of Radiology, in Chicago, in September, 1933 (2), summarizing the treatment of 134 cases of generalized neoplasms, including the 44 cases of Hodgkin's disease. In regard to this disease it was concluded that irradiation of the entire body appeared to be a valuable adjunct to local irradiation, although not satisfactory as the sole method of irradiation. Bulky masses could not be satisfactorily treated by local irradiation, but if the main foci were satisfactorily treated by local irradiation, the addition of small doses of general irradiation seemed to contribute sometimes a certain tonic effect, and some of the patients seemed to have longer periods of freedom from renewed disease activity than they would otherwise have been expected to have. These results were attributed mainly to the effects on small latent or obscure foci which would not have been reached by local treatments.

In June, 1935, a second Heublein unit was installed on a more economical basis, and is still in use, so that we have had over two years' further experience with this method. Reviewing the work with the first unit, we felt our experience with it had been sufficient to establish fairly well that its field of usefulness was as an adjunct to local therapy. Therefore, in employing the new unit we have taken the position that it would be unfair to patients to restrict their treatment to general irradiation in a further attempt to see what it alone would do, and accordingly all cases treated by the second unit have also had local irradiation, before, during, or after the general treatment. Naturally it is very difficult to differentiate between the effects produced by local irradiation and those due to treatment of the entire body.

We have treated with the second unit, up to April 18, 1937, 45 patients with Hodgkin's disease. Of these, four had been treated previously with the old unit, so that we have a grand total of 44 plus 41, or 85 patients treated by this method.

Of the 44 patients treated by the first Heublein unit, ten are still living, from four to nearly six years following that treatment. Only two of these ten patients are in poor condition. Two appear to have no disease activity, four and a third years following the first Heublein treatment. These two, and two others of the ten, have had treatment by the new as well as by the old unit.

As to the results from our second period of use of this method, during the past two years, it is impossible to give statistics because of the fact that local irradiation has also been used. It seems safe to state, however, that the impressions gained as a result of use of the former unit have been confirmed in many instances. In other words, although the general irradiation is usually followed by a period of weakness, leukopenia, and some anemia, there is frequently observed later a tonic effect, with gain of weight, some degree of regression of enlarged lymph nodes, and a longer interval before further treatment becomes necessary than could otherwise be expected.

In treating Hodgkin's disease at Memorial Hospital we have concentrated our efforts on close observation of our patients, on a search for obscure lesions, and on seeking to improve our technic of irradiation. Such results as we have are attributed to these efforts. We speak of five-year results as "survivals" rather than "cures." A recent analysis of our cases admitted between Jan. 1, 1918, and Dec. 31, 1930, and carrying results up to Dec. 31, 1935, has rejected a few cases formerly accepted as proven by biopsy, leaving 121 cases regarded as so proven. Of this group, 21 patients (or 17 per cent) survived for five years or longer (Table II).

TABLE II.—FIVE-YEAR SURVIVALS IN HODGKIN'S DISEASE

Admitted Jan. 1, 1918, to Dec. 31, 1930

| Total No. Proved by Biopsy | Five-year Survivals | |
|---|---|---|
| | No. | Per Cent |
| 121 | 21 | 17 |

## SUMMARY

1. The treatment of Hodgkin's disease by modern standards is much more com-

plex than the irradiation simply of certain lymph node areas.

2. The great diversity of lesions found in this disease will probably always inhibit the establishment of any routine as the treatment of choice.

3. While different technics may produce palliation, a review of the cases treated at Memorial Hospital leads to an impression that in local irradiation the use, wherever feasible, of fewer but larger doses may, in general, be preferable to protracted cycles of fractional dosage.

4. Irradiation of the entire body appears to have a definite place as an adjunct to local irradiation in the treatment of Hodgkin's disease.

5. Of 121 proven cases of Hodgkin's disease, 17 per cent showed a survival of five years or longer.

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# OBSERVATIONS ON THE RADIOLOGICAL CHEST VOLUME DURING ARTIFICIAL PNEUMOPERITONEUM TREATMENT

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THERE is no report in the medical literature dealing with the effect of artificial pneumoperitoneum upon the volume of the lung. The object of this paper is the presentation of the results of an investigation concerning this problem. Since 1929, when I began to use pneumoperitoneum for the treatment of tuberculous enterocolitis, I have observed that in some of my patients not only the intestinal condition improved but also symptoms originating from their pulmonary tuberculosis were favorably influenced. These observations were reported by me in 1931 (1). At the same time the problem of treating pulmonary tuberculosis by artificial pneumoperitoneum was also discussed. This treatment has been in use at Muirdale Sanatorium since that time either as an independent therapeutic measure or in combination with surgical paralysis of the phrenic nerve (2). It is used mainly in cases in which other local mechanical measures, such as artificial pneumothorax, phrenic nerve block, or thoracoplasty are technically impossible, unsatisfactory, or contra-indicated. In several of my pneumoperitoneum patients artificial pneumothorax failed either because there was no free pleural space when the injection was first attempted or because the pleural space became obliterated by adhesions during pneumothorax treatment. Pneumoperitoneum proved to be of value in patients in whom a bilateral treatment was indicated, but the extensive involvement of both lungs contra-indicated a bilateral artificial pneumothorax. Patients past 50 years of age tolerate pneumoperitoneum treatment better than bilateral pneumothorax. Basal forms of pulmonary tuberculosis respond particularly well to pneumoperitoneum. Furthermore, it may be of some value in patients in whom thoracoplasty would be the treatment of choice, but is disregarded because of the age or general debility of the patient, or because of the bilateral extent of the disease. Some benefit from this treatment may be expected in patients who refuse to accept thoracoplasty.

The subjective and objective responses to this treatment have been reported in previous communications (3). It may be stated briefly that favorable changes in the character, severity, frequency, and duration of cough were noted. At the beginning, the amount of sputum is increased, but, as a rule, it is expectorated with less effort and strain, while it is likely to decrease substantially during the subsequent course of the treatment. Patients who respond well, show roentgenologic evidence of clearing of the tuberculous process, sometimes diminution in size or closure of cavities. Concomitant changes in the patient's general condition were often observed, such as the disappearance of malaise, increased appetite, and gain in strength and weight.

The clinical improvement in some of my patients was comparable with that seen after artificial pneumothorax or phrenic nerve block. On the basis of analogy one is justified in assuming that the therapeutic effect of pneumoperitoneum must be actuated by the same factors that are active in pneumothorax and phrenic nerve block. The most important of these factors are: (1) relaxation of the diseased lung tissue; (2) relative passive congestion, and (3) lymph stasis. Pulmonary relaxation facilitates the drainage and elimination of muco-purulent products from the bronchial tract. A relative passive congestion signifies the presence of a large number of defense elements of the blood, and an increased carbon dioxide concentration. The potential benefits of the latter were presented in a previous paper (4). Lymph

stasis favors fibrous tissue formation.

This study was undertaken for the purpose of ascertaining accurately the presence and extent of pulmonary relaxation during pneumoperitoneum treatment. The estimation of the radiological chest volume was thought to be the most suitable procedure. This method was described by Hurtado and Fray in 1933 (5). They found that the best approximate value of the chest cavity could be obtained from combined external and radiological measurements. The radiological chest volume is calculated by multiplying the area of the lung-fields, including the heart, measured in radiological films, by the anteroposterior diameter of the chest determined externally. In the present study the original method of Hurtado and Fray was somewhat modified. Films were taken at the end of maximum inspiration and expiration, from a distance of six feet, with the patient in the upright position. The area of the right and left lung was measured separately. It was outlined by marking the upper margin of the apices, the inner margin of the ribs, and the dome of the diaphragm. The line separating the two lungs was drawn

TABLE I.—NUMBER OF INSTANCES WITH REDUCTION OF THE RADIOLOGICAL CHEST

| Number of Treatments | More Diseased Lung | | | | Less Diseased Lung | | | | R. Lung, Disease Same as in L. Lung | | | | L. Lung, Disease Same as in R. Lung | | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Reduction | | No Reduction | | Reduction | | No Reduction | | Reduction | | No Reduction | | Reduction | | No Reduction | | |
| | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | |
| 1 | 13 | 9 | 2 | 6 | 10 | 8 | 5 | 7 | 2 | 2 | | | 2 | 1 | | 1 | 68 |
| 3 | | | | 1 | 4 | 1 | | 3 | 1 | 1 | | | 1 | 1 | | | 4 |
| 4 | 4 | 3 | | | 1 | | | | | | | | | | | | 16 |
| 5 | | 1 | 1 | | 2 | | | 1 | | | | | | | | | 4 |
| 6 | 2 | 2 | | | 1 | 1 | 1 | | | | | | | | | | 8 |
| 7 | 1 | 1 | | | | 1 | 1 | | | | | | | | | | 4 |
| 8 | | 1 | 1 | | | 1 | 1 | | | | | | | | | | 4 |
| 9 | 3 | 3 | | | 2 | 3 | 1 | | | | | | | | | | 12 |
| 10 | 3 | 3 | | | 3 | 2 | | 1 | | | | | | | | | 12 |
| 12 | 1 | 1 | | | 1 | 1 | | | | | | | | | | | 4 |
| 13 | 2 | 2 | | | 2 | 1 | | 1 | | | | | | | | | 8 |
| 14 | 2 | 2 | | | 1 | 2 | 1 | | | | | | | | | | 8 |
| 15 | 5 | 4 | 1 | | 3 | 5 | 2 | | 2 | 3 | 1 | | 3 | 3 | | | 32 |
| 16 | 1 | 2 | | | 1 | 1 | 1 | 1 | 1 | 1 | | | 1 | 1 | | | 12 |
| 17 | 2 | 2 | | | 2 | 1 | | 1 | | | | | | | | | 8 |
| 19 | 4 | 4 | | | 3 | 4 | 1 | | | | | | | | | | 16 |
| 20 | 1 | | 1 | | 1 | 1 | | | | | | | | | | | 4 |
| 21 | 2 | 2 | 1 | | 3 | 2 | | 1 | | | | | | | | | 12 |
| 25 | 1 | 1 | | | 1 | 1 | | | | | | | | | | 1 | 4 |
| Total | 47 | 43 | 6 | 10 | 40 | 36 | 14 | 16 | 6 | 7 | 1 | | 7 | 6 | 1 | 1 | 240 |
| Total | 90 | | 16 | | 76 | | 30 | | 13 | | 1 | | 13 | | 1 | | |

Abbreviations: R = right; L = left.

along the middle of the trachea and mediastinum. The measurements were made with the aid of a planimeter, the tracer arm of which was carried along the circumference of the lung. The figures on the differential wheel of the planimeter indicated areas in square centimeters.

An unselected group of 40 patients was studied, all of whom were receiving pneumoperitoneum for the treatment of their pulmonary tuberculosis. Of these patients, eight had moderately advanced and 32 far advanced tuberculosis according to the classification of the National Tuberculosis Association. The amount of injected air varied from 500 to 1,000 c.c. at each treatment. The injections were given at weekly intervals at the beginning, and two weeks apart when the pneumoperitoneum was well established.

The radiological chest volume was measured in 17 instances after the first treatment, in one after the third, in four after the fourth, in one after the fifth, in two after the sixth, in one after the seventh, in one after the eighth, in three after the ninth, in three after the tenth, in one after the twelfth, in two after the thirteenth, in two after the fourteenth, in eight after the fifteenth, in three after the sixteenth, in two after the seventeenth, in four after the nineteenth, in one after the twentieth, in three after the twenty-first, and in one after the twenty-fifth treatment. These represent a total of 60 instances, each with four measurements. Including 160 measurements made before the treatment, altogether 400 measurements were analyzed. The results are presented in Tables I and II.

It was found that in cases with bilateral pulmonary involvement a reduction in the volume of more diseased lung was rather more frequent than in that of the less diseased lung. The explanation of this difference can be found in the increased contractility of the more involved lung tissue. To the same factor is attributable the fact that reduction of the pulmonary volume was absent in almost twice as many instances on the less diseased side than on the more diseased side. In the latter group, out of 106 observations, reduction was absent in 16 (15 per cent), while in the former group, with the same number of observations, it was absent in 30 (28.3 per cent).

TABLE II.—MAXIMUM REDUCTION OF THE RADIOLOGICAL CHEST VOLUME

| Number of Treatments | More Diseased Lung | | | | Less Diseased Lung | | | | Equal Disease in Both Lungs | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Reduction | | No Reduction | | Reduction | | No Reduction | | Reduction | | No Reduction | |
| | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. | Inspir. | Expir. |
| 1 | 15 | 11 | 2 | 6 | 13 | 27 | 5 | 7 | 6 | 4 | | 1 |
| 3 | 2 | 11 | | | | | | | 13 | 8 | | |
| 4 | 2 | 11 | | 1 | 8 | 9 | | 3 | | | | |
| 5 | | 4 | 1 | | 3 | 13 | 1 | 1 | | | | |
| 6 | 24* | 15* | | | 3 | 13 | 1 | | | | | |
| 7 | 11 | 7 | | | | 8 | 1 | | | | | |
| 8 | 19 | | 1 | | | 4 | 1 | | | | | |
| 9 | 14 | 10 | | | 16 | 13 | 1 | | | | | |
| 10 | 21* | 14 | | | 10 | 11 | | 1 | | | | |
| 12 | 13 | 12 | | | 18 | 9 | | | | | | |
| 13 | 32* | 57* | | | 10 | 17 | | 1 | | | | |
| 14 | 7* | 21* | | | 3 | 7 | 1 | | | | | |
| 15 | 39* | 49* | | 1 | 23 | 34 | 2 | | 24 | 25 | 1 | |
| 16 | 3 | 6 | 1 | | 8 | 18 | 1 | 1 | 22 | 19 | | |
| 17 | 14 | 15 | | | 9 | 8 | | 1 | | | | |
| 19 | 34 | 35 | | | 18 | 46 | 1 | | | | | |
| 20 | 1 | | | 1 | 4 | 1 | | | | | | |
| 21 | 11 | 6 | 1 | 1 | 6 | 9 | | 1 | | | | |
| 25 | 6 | 5 | | | 5 | 13 | | | | | | |

* Phrenic nerve block and pneumoperitoneum.

In patients who had about equal involvement of the two lungs, reduction of the volume or absence of reduction were seen in an equal number of instances on the two sides.

Following the first treatment, 68 measurements were made. The more diseased lung showed a reduction of the volume on inspiration in 13 instances, and on expiration in nine instances out of a total of 15. This reduction is responsible for the oftentimes markedly increased amount of expectorated muco-purulent material following the institution of pneumoperitoneum treatment.

As to the degree of reduction of the lung volume three observations are noteworthy:

1. When pneumoperitoneum treatment is continued for a reasonable length of time (two months or longer), a therapeutically satisfactory reduction of the lung volume can be established, with the exception of relatively few cases in which extensive pleural adhesions prevent the rise of the diaphragm.

2. Not all patients show equal results with equal amounts of injected air and after equal number of treatments. The marked differences are attributable to the type and extent of the tuberculous lesion, the presence or absence of pleural adhesions, and the abdominal accommodation. Injection of substantial amounts of air into the abdominal cavity is followed by an increased intra-abdominal pressure. The latter is followed by a reflex relaxation of the abdominal wall, and by a rise of the diaphragm. Variations in this reflex and in the tonicity of the muscles of the abdominal wall and the diaphragm are responsible for the variations in the abdominal accommodation and in the consequent reduction of the lung volume. Thus, it is readily understandable why this reduction is not predictable and why the accompanying pulmonary relaxation is not as easily manageable as pulmonary collapse during artificial pneumothorax treatment.

3. The combination of the surgical paralysis of the phrenic nerve with pneumoperitoneum is far superior to either of these procedures alone. The greatest reduction of the pulmonary volume was seen in instances in which this combination treatment was employed.

The maximum reduction of the volume after ten or more treatments was, on inspiration, 34 per cent and, on expiration, 35 per cent without a phrenic nerve block. According to my experience such a marked relaxation of the lung without phrenic nerve surgery is the exception rather than the rule. The average reduction of the lung volume after ten or more treatments was, on the more diseased side, 11.3 per cent on inspiration and 15.6 per cent on expiration; on the less diseased side the corresponding figures were 8.7 per cent and 14 per cent, respectively.

## CONCLUSIONS

1. Four hundred measurements were made for the purpose of ascertaining the effect of pneumoperitoneum upon the lung volume.

2. Evidence is presented that the sustained use of artificial pneumoperitoneum treatment is capable of inducing an elevation of the diaphragm and a reduction of the lung volume in the great majority of cases.

3. The beneficial results in the treatment of certain types of pulmonary tuberculosis by artificial pneumoperitoneum are attributable to the reduction of the lung volume and to the consequent relaxation of the diseased lung.

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# SOME BIOLOGICAL EXPERIMENTS WITH A CONDENSER DISCHARGE TYPE OF X-RAY TUBE

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THE question of the validity of the ordinary Bunsen-Roscoe reciprocity law for the biological effects of radiation has long been a moot one, and satisfactory evidence on either side has not been forthcoming. The principal reason for its absence has lain in the lack of availability of suitable physical equipment, which would permit a sufficient increase in the intensity of applied x-radiation to test the law over a very large range.

Such equipment has recently been designed by Kingdon and Tanis and described by them (1). They have shown that a large and reproducible x-ray emission may be obtained by discharging a condenser through a tube containing a tungsten anode and a liquid-air-cooled mercury-pool cathode. The peak of current obtained through the tube under these conditions reaches several hundred amperes, so that the instantaneous x-ray intensity produced is extremely high.

The availability of this radiation source has made possible the conducting of a number of radiation experiments with very carefully standardized biological materials which, it is felt by the writers, are rather conclusive in their bearing upon the reciprocity problem. Some experiments have also been conducted in which very intense magnetic fields have been used in conjunction with x-radiation in biological problems, the physical equipment being of such character as to make this work also rather definitive, it is thought. It is the purpose of this paper to describe this work, first in relation to high intensity radiation, and second in connection with the imposing of high intensity magnetic fields during radiation.

*Sources and Character of Radiation.*—The source of high intensity radiation used in the experiments to be described was a mercury-pool cathode x-ray tube operated from a 0.025 microfarad condenser charged to 105 kv. and discharged through the tube. Each discharge delivered 3.5 roentgens of radiation in a period of about $5 \times 10^{-6}$ sec. at a point 11.5 cm. from the target. The condenser was discharged about once per second, so that the instantaneous x-ray emission reached $4.2 \times 10^{7}$ r/min., while the average rate was 200 r/min.

In order to measure these high intensities of radiation a Victoreen dosimeter was placed at a considerable distance from the target (about 50 cm.), and the dose at the specimen calculated from the inverse square law. A dosimeter placed at the position of the specimen read only about half of the calculated value because of ion recombination in the chamber. A dosimeter with a smaller chamber read about two-thirds of the calculated dosage.

As a control source of radiation a Coolidge tube was used, with tungsten target, operated with a manually controlled switch to provide intermittent running. The current through the Coolidge tube was maintained at from 1 to 2 ma.

*Materials and Methods.*—Three biological test objects were used in the work; the first, a strain of thoroughly standardized eosin stock of *Drosophila melanogaster*, long used by one of us (2) in x-ray experiments of a different nature; the second, a standardized strain of *Aspergillus niger*, prepared for use in experiments with low voltage cathode rays now in progress and partially published (3), and the third, seeds of a stock of winter wheat. Failure of irradiated eggs to hatch was used as the criterion of effect with *Drosophila*, and failure to produce a visible mycelium with *Aspergillus*, while in the case of wheat the lengths of coleoptiles and roots of irradiated seeds were measured, and their

diminution constituted a measure of the effectiveness of the radiation.

*Drosophila Eggs.*—Eggs were collected on agar disks sprayed with a suspension of yeast, and the disks were mounted on

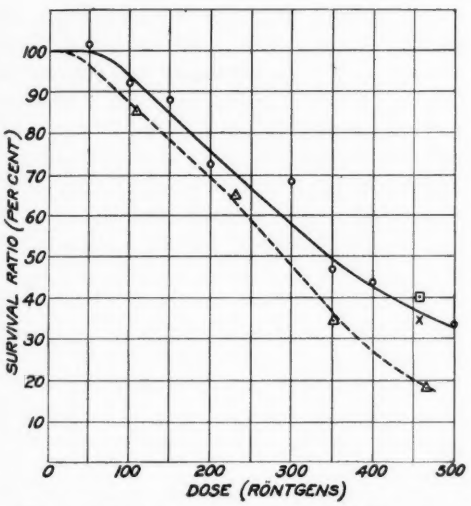


Fig. 1. Survival of eggs of *Drosophila melanogaster* as a function of x-ray dosage (full curve). The dotted curve shows comparable data from Henshaw and Henshaw.

cellophane sheets prior to radiation. All eggs were rayed at an age of less than two hours, the usual precautions being taken against the confusion of fresh with retained eggs. The percentage of survival of eggs was determined with a dissecting microscope 48 hours after irradiation, when all normal, or even considerably delayed, eggs would have hatched. The raying was done at various times between Aug. 18 and Sept. 18, 1937, and controls were run at intervals throughout this period. All raying was done at 105 kv. The data are shown in Table I, and are plotted in Figure 1. Figure 1 also includes a curve (dotted) showing the data of Henshaw and Henshaw (4) for the x-ray killing of eggs of *Drosophila* of the same age range as ours (0–2 hours). Apparently the eggs of the eosin strain of flies used by us were somewhat more resistant to x-rays than the stock used by Henshaw and Henshaw.

For all runs made at such distance from the tube that the applied dosage was 0.33 r/shot the eggs were enclosed in a grounded aluminum case 0.05 cm. in thickness to protect the material from electrical effects due to the violent change in potential accompanying the condenser discharge. This precaution was shown by the experiments to be unnecessary, so that in the data given in the last line the material was moved closer to the tube and the dosage increased to 3.3 r/shot. This point, indicated by a square, falls close to the others in Figure 1. The comparison run with the Coolidge tube was made with the same condenser discharged through it, at an average current of 2 ma. and with the eggs at such a distance that the dosage was 3.5 r/shot, so that the data are very nearly strictly comparable. This point is shown as a cross in Figure 1, and lies close to the curve through the other points. The conclusion may fairly be drawn that a given dosage of x-rays pro-

TABLE I

| Tube Used | Roentgens/Shot | Total Dosage in r | No. Eggs | No. Eggs Surviving | Percentage of Survivals | Survival Ratio |
|---|---|---|---|---|---|---|
| Mercury | 0.33 | 50 | 771 | 713 | 92.5 | 101.6 |
| " | 0.33 | 100 | 806 | 672 | 83.4 | 91.8 |
| " | 0.33 | 150 | 811 | 649 | 80.1 | 87.9 |
| " | 0.33 | 200 | 1,325 | 875 | 66.1 | 72.7 |
| " | 0.33 | 300 | 824 | 513 | 62.3 | 68.5 |
| " | 0.33 | 350 | 929 | 394 | 42.1 | 46.7 |
| " | 0.33 | 400 | 889 | 357 | 40.2 | 44.2 |
| " | 0.33 | 500 | 790 | 245 | 31.1 | 34.2 |
| " | 0.00 | 0 | 2,294 | 2,085 | 90.9 | 100.0 |
| Coolidge | 3.5 | 467 | 721 | 231 | 32.1 | 35.3 |
| Mercury | 3.3 | 467 | 678 | 251 | 37.1 | 40.9 |

Fig. 2. Killed and germinating spores of *Aspergillus niger*. These spores have grown to a stage beyond that desirable for counting.

duces the same effect in killing the eggs of *Drosophila* whether it is delivered in low intensity (2 ma. current) or in high intensity (400-amp. current) pulses.

*Aspergillus Niger.*—Dormant spores of *Aspergillus niger* of about two weeks of age were dusted onto narrow strips of cellophane, and four strips were mounted side by side inside the ungrounded aluminum case in front of the mercury pool cathode x-ray tube. The condenser was charged to 105 kv., and the spores received 3.4 r of x-rays per shot. When a desired dosage for one sample had been reached, it was removed and irradiation continued for the remainder. The spores were printed from the cellophane onto blocks of potato-maltose agar, and incubated for about eight hours at 30° C., after which counts were made of the number in which a mycelial beak had appeared, the low power of a microscope being used for this purpose. Figure 2 shows a photomicrograph of dead and growing spores after longer incubation (20 hours).

The experiment was repeated on the following day with the Coolidge tube. Large dosages being necessary for this experiment, the condenser was not used, since each discharge required the manual

TABLE II

| Mercury-pool Cathode Tube | | | Coolidge Tube | | |
|---|---|---|---|---|---|
| Dosage | Percentage of Survival | Survival Ratio | Dosage | Percentage of Survival | Survival Ratio |
| 0 r | 86.4 | 100.0 | 0 r | 80.9 | 100.0 |
| 1,000 | 66.5 | 77.0 | 1,100 | 68.0 | 84.1 |
| 3,000 | 62.4 | 72.3 | 3,370 | 65.3 | 80.8 |
| 6,000 | 42.1 | 48.8 | 6,795 | 47.8 | 59.1 |
| 10,000 | 32.6 | 37.8 | 11,245 | 22.4 | 27.7 |

TABLE III

| Mercury-pool Cathode Tube | | | | Coolidge Tube | | | |
|---|---|---|---|---|---|---|---|
| Dosage | No. of Seeds | Ave. Length of Coleoptile | Survival Ratio (Percentage Average Length in Controls) | Dosage | No. of Seeds | Ave. Length of Coleoptile | Survival Ratio (Percentage Average Length in Controls) |
| 0 r | 68 | 30.5 mm. | 100.0 | | | | |
| 1,000 | 29 | 23.5 | 77.0 | 1,000 r | 30 | 24.5 | 80.3 |
| 2,000 | 30 | 20.3 | 66.5 | 2,000 | 30 | 17.8 | 58.4 |

There is no significant difference between the results for the two tubes.

opening and closing of a switch, a condition not required by the set-up of the mercury-pool tube. The Coolidge tube was, therefore, run continuously at a potential of 90 kv., this potential being chosen to give approximately the same quality of radiation as that coming on the average from the condenser discharge through the mercury-pool tube. The current through the tube was 1.5 ma. The data for the two experiments are shown in Table II, and are plotted in Figure 3.

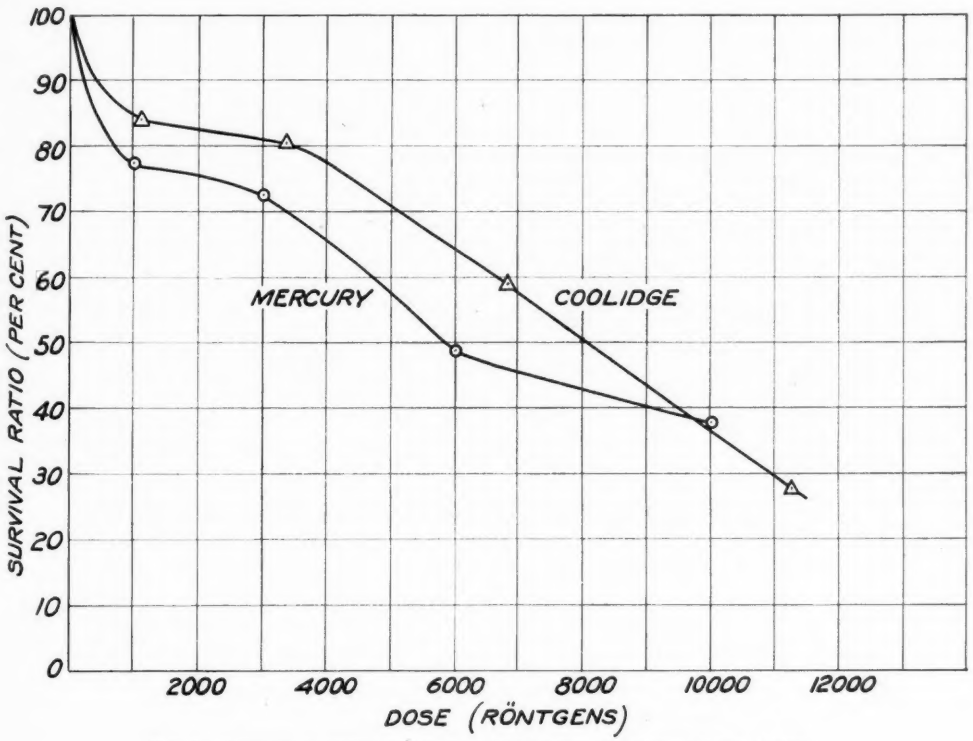


Fig. 3. Survival of spores of *Aspergillus niger* as a function of x-ray dosage.

About 700 spores were counted for each point. Counting was rendered difficult by the high density of spores in some fields, and it is not thought that there is any significant difference between the two curves, indicating substantially equal effectiveness of the two types of radiation.

*Wheat Seedlings.*—Seeds of white winter wheat were soaked in tap water for 3 hours and set to germinate in a moist Petri dish. They were rayed about 18 hours after having been put to soak. Both the mercury-pool tube and the Coolidge tube were used with the condenser charged to 105 kv. and the dosage per shot for both tubes 3.4 r. The peak current for the mercury tube, as before, was about 400 amperes, while that of the Coolidge tube was 1.5 ma., so that there was a ratio of about $2.6 \times 10^5$ between the instantaneous x-ray intensities of the two tubes.

The biological criterion used was length of coleoptile of the young seedling, which was measured 74 hours after the seeds were put to soak. The results are shown in Table III.

## DISCUSSION

The results presented above are in agreement with the work of others, using lower

intensities, who have found that the biological effects of x-rays are nearly independent of the instantaneous intensity, unless the dosages are spaced sufficiently far apart to permit of biological recovery, which was not the case here.

Contrary to such a conclusion are the experiments reported by Lawrence, Zirkle, and their associates (5) in which the greater efficiency of neutrons in killing certain organisms is accounted for by the high intensity of ionization occurring along the track of a proton. Their experiments have shown that a given dosage of neutrons, as measured by a Victoreen dosimeter, produces a larger biological effect than an equivalent dosage of x-rays as measured by the same instrument.

These differing experimental results may be at least partially accounted for by assuming that the changing or killing of a living cell is due to the production of ionization (or excitation) in extremely small, discrete volumes within it, volumes of the order of magnitude of a single gene (radius, on the assumption of sphericity, of the order of $5 \times 10^{-7}$ cm.) and by considering the distribution of ionization along the paths of an electron and a proton. The latter point is discussed in some detail in the paper of Kingdon and Tanis already referred to (1), and Figure 3 is taken from that paper. In this figure the two upper lines, taken in series, represent the ionization occurring along the path of a $3 \times 10^4$ volt electron going through tissue which is taken to be 800 times as dense as air at n.t.p. Each dot represents a pair of ions (+ and −). Cloud chamber photographs in air indicate that pairs of ions may be produced singly, or may occur in groups of two or more pairs. Actually, these groups of ion pairs are spaced at random intervals—in the figure they are drawn at a constant average distance apart. Similarly the numbers of dots in each group are taken to represent the average distribution of numbers of ion pairs in the groups along the track. The scale of distances is the same on both abscissa and ordinate, so that the spacing of dots in any one group is, for electrons, predominantly closer than the spacing of groups themselves.

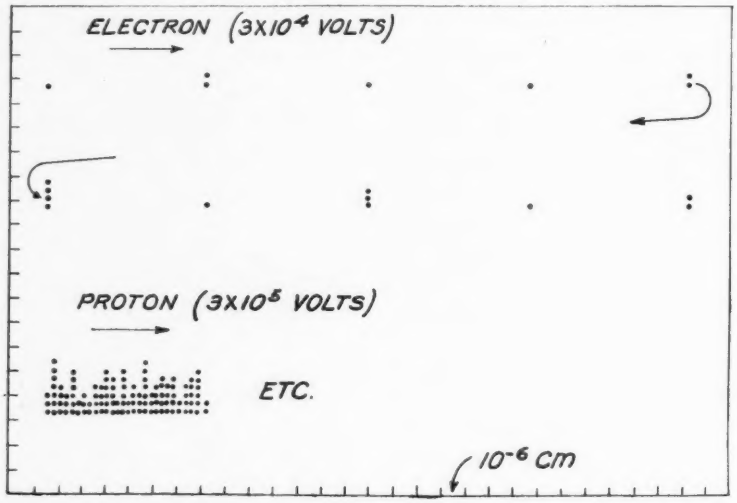


Fig. 4. Distribution of ionization along the paths of an electron and a proton in body tissue.

Below is shown a similar plot of the ionization along the path of a proton of $3 \times 10^6$ volts in the same tissue. The energies assumed may be taken as typical for particles with which we are concerned.

If the biological killing effect of radiation is due to the production of a single ion pair in a volume of the order of magnitude of that of a gene (say, dimensions of $5 \times 10^{-7}$ cm.), then on the basis of Figure 3 one would expect no appreciable difference in efficiency between electron and proton ionization. By far the greater portion of the ionization will be wasted, as it occurs in tissue outside the "sensitive volume," so that it would make no difference if a proton wasted a little more of its energy by producing two or three ion pairs in cases in which only one was needed. On the other hand, if the interaction requires the simultaneous production of two ion pairs in a "sensitive volume," protons should be about twice as efficient as electrons, since in only about 50 per cent of the electron ionizations can two ion pairs be produced within the "sensitive volume." This increase in efficiency is of the order reported for the neutron experiments.

Most of the experiments with the mercury-pool cathode x-ray tube were done using shots of 3.5 r delivered in $5 \times 10^{-6}$ sec. If the ions resulting from each shot are considered to be made simultaneously, we can estimate whether their concentration is sufficient to expect differing biological effects on the basis of Figure 3. Assuming tissue to be 800 times as dense as air at atmospheric pressure, the number of ions produced in 1 c.c. of tissue for a dosage of 3.5 r will be $5.9 \times 10^{12}$, and the average distance between these ions will be $5.4 \times 10^{-5}$ cm. Thus the space between tracks of individual high speed electrons will be large compared with the spacing of ions along any one track, and on the basis of Figure 3 the x-rays from the mercury-pool cathode tube should behave biologically like x-rays of ordinary intensity.

*The Effect of High Intensity Magnetic Fields.*—The biological experiments with neutrons from the cyclotron have been performed in the strong fringing magnetic field of the cyclotron. It was felt that the presence of this field might possibly produce appreciable changes in the energy levels of the molecules comprising the

TABLE IV.—WHEAT SEEDLINGS

| X-ray Dosage | Strength of Field | No. Seeds | Average Total Root Length | Average Total Coleoptile Length |
|---|---|---|---|---|
| 550 r | 23,000 oersteds | 23 | 74.6 mm. | 24.2 mm. |
| 550 | 0 | 23 | 56.8 | 19.7 |
| 0 | 0 | 20 | 117.7 | 30.8 |

TABLE V.—*Aspergillus* SPORES

| X-ray Dosage | Strength of Field | No. Spores | Percentage of Survivals | Survival Ratio (per cent) |
|---|---|---|---|---|
| 6,023 r | 15,000 oersteds | 536 | 53.9 | 60.1 |
| 0 | 0 | 442 | 89.6 | 100.0 |
| 6,028 | 0 | 567 | 42.9 | 47.3 |
| 0 | 0 | 642 | 90.8 | 100.0 |
| 6,004 | 15,000 | 434 | 52.9 | 57.5 |
| 0 | 0 | 437 | 92.0 | 100.0 |
| 6,013 | 0 | 512 | 62.9 | 68.4 |
| 0 | 0 | 498 | 92.0 | 100.0 |

TABLE VI.—*Drosophila* EGGS

| X-ray Dosage | Strength of Field | No. Eggs | Percentage of Survivals |
|---|---|---|---|
| 292 | 0 oersteds | 96 | 63.5 |
| 287 | 23,000 | 105 | 66.6 |

"sensitive volume" (as in the Zeeman effect for atoms and molecules) and so increase the biological effectiveness of the radiation. Such a possibility, though remote, seemed worth testing.

A series of rough experiments was made for this purpose with x-rays from the Coolidge tube, using the stocks of wheat seedlings, *Aspergillus* spores, and *Drosophila* eggs already described. The results are shown in Tables IV, V, and VI.

In no case did the magnetic field produce a significant change in the survival. This is in agreement with the fact that the changes in energy levels as determined from Zeeman effect measurements are very small. For the fields used the maximum change in energy of a level is of the order of a few tenths of a millivolt, and as this is probably very small compared with the total energy of a level, no significant change in the target area of the molecule would be expected.

SUMMARY

Biological experiments are described using a condenser discharge x-ray tube capable of delivering a dose of 3.5 roentgens in five micro-seconds. Tests have been made of the validity of the Bunsen-Roscoe reciprocity law with eggs of *Drosophila melanogaster*, spores of *Aspergillus niger*, and wheat seedlings, a Coolidge tube operated at normal intensity being used as the source of radiation for the controls. No significant differences were found in the two sets of experiments, indicating the validity of the law over the range tested.

Experiments have been made with the x-rayed material held in intense magnetic fields up to 23,000 oersteds, using the radiation from the Coolidge tube already mentioned, and the same biological materials. No appreciable effect of the magnetic field was found.

Some implications of the work are considered.

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# BONE (CALCIUM) METABOLISM IN RELATION TO INDUSTRIAL INJURY[1]

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DURING the past decade, stimulated by the work of Leriche and Policard, an enormous amount of research has been done on the physiology and metabolism of bone. It would require all the time allotted this paper simply to read the list of articles which have appeared in European and American medical journals on this subject: many notable contributions have been made which cannot even be mentioned by name in so brief a summary. These researches have brought about a complete revision in our conception of bone tissue, bone metabolism, and bone repair, but the newer facts have not yet been appropriated and utilized in the field where they are most needed, namely, that of industrial injuries.

Since the repair of a bone defect produced by injury or disease is simply a modification of the osteogenesis by which bone was originally formed, the importance which Leriche and Policard attach to this physiological process is justified. The old anatomical teaching persists in our minds that bone is the framework of the body, designed solely to support the softer tissues and provide for locomotion and other muscular actions. Usually our treatment of injuries is based on this concept of bone as a fixed and stable tissue which gradually reaches mature development and then maintains its form, structure, and mineral content unchanged, unless some injury or destructive disease attacks it. One of the most important observations of modern physiology is that no tissue in the body, with the possible exception of the blood, undergoes more rapid and striking changes, from a greater variety of influences, than the bone structure.

A better understanding of the importance of calcium and phosphorus metabolism has resulted from the investigations of the past decade. Once regarded as inert minerals whose sole function was to give hardness and stability to the bones, the salts of these elements are now known to be essential and vital in the general metabolism. They are in such constant demand that a supply is stored in the bones. Leriche and Policard advance the intriguing suggestion that calcium is necessary for normal life processes and its storage must have been provided for in the very earliest stages of evolution, millions of years before locomotion entered the scheme; therefore, the deposition of calcium for storage purposes to provide for future metabolic demands must have preceded the utilization of such depots of calcium as a means of support for soft tissues and as levers for muscular movements. The functions of support and locomotion which we regard as the chief purposes of the skeletal framework were, according to this suggestion, late and fortuitous developments in the process of evolution. That idea is not only philosophic but is in line with the recently acquired knowledge that calcium is needed in the body for many other purposes besides giving stability to the skeleton, and when so needed it is rapidly removed from the bones, regardless of the effect on locomotion and support. When we place our trust in Nature to aid in healing bone injuries, we must remember that she regards the functions of locomotion and support as of secondary importance when calcium is required for more vital needs.

Our present-day concept of osteogenesis involves the deposition of calcium in a preformed connective tissue matrix. Whether we are considering the development of bone in the growing organism, or studying the repair of bone defects produced by injury or disease, osteogenesis requires the con-

[1] Presented before the Fifth International Congress of Radiology, at Chicago, Sept. 13–17, 1937.

verging action or concatenation of two groups of factors; one group includes the systemic or metabolic influences and the other includes the local factors. The systemic factors are (*a*) fundamental cellular differentiation; (*b*) calcium and phosphorus supply; (*c*) action of vitamin D; (*d*) parathormone control; (*e*) indirect metabolic influences. The local factors are (*a*) vascular supply; (*b*) cellular activity; (*c*) phosphatase action; (*d*) neurotrophic control; (*e*) mechanical demands. Normal osteogenesis will not take place if any one of these general or local factors is lacking. Whether one is a clinician attempting to guide the normal development of a growing individual, or a surgeon seeking to bring about repair of an injury or disease in bone, it is important that these ten factors be understood and their active participation secured.

### SYSTEMIC FACTORS

(*a*) *Fundamental Cellular Differentiation.*—The old argument over the relative merits of the cellular or humoral theories of calcium deposition may never be settled, but there is no question about the origin of bone through differentiation of the primitive embryonic cells. It is an histologic fact that bone is modified connective tissue, arising originally from mesodermic cells by differentiation. It is also generally accepted that these cells first differentiate into embryonal connective tissue and from this basic type all other forms of connective tissue arise—reticular, areolar, adipose, fibrous, cartilage, and bone. When connective tissue first begins to develop in the embryo, we do not of course have all ten of these factors converging to produce bone. We have then only the phylogenetic and ontogenetic forces of evolution and heredity at work, and concerning these we have little knowledge. Until we can explain life itself, we have no explanation for the teleologic forces which initiate and carry on cellular differentiation in the embryo. Biologists dislike the term "teleology" in connection with cell activity, but until some other hypothesis is brought forth to explain why cells differentiate, we can say only that the life purpose of the cell causes it to act as it does, and this purpose underlies any functional adaptation.

Passing by this point which is of more philosophic than practical interest, we can start with the known fact that bone is developed out of embryonic connective tissue. Whether the cells of this primitive tissue differentiate further into osteoblasts with the function of laying down calcium as a secretion, or whether the calcium is deposited mechanically in the matrix of the embryonal tissue is another unsettled point, but again, and fortunately, of academic interest only. The question which does seem to be settled is that we must have a preformed connective tissue matrix in which calcium and phosphorus can be deposited, before bone tissue will develop. While calcium may deposit in any kind of connective tissue, the more primitive this matrix is the more perfect and normal will be the resulting bone. Therefore, bone which forms in embryonic or reticular connective tissue will be more nearly normal than that which forms in fibrous or fatty tissue. Every wound in the body tissues is repaired by the formation of embryonic (granulation) connective tissue, even though this be microscopic in amount. Following the reaction of repair and development of granulation tissue, this is converted into the form of differentiated connective tissue determined by the local factors. Therefore, in the repair of bone injuries, just as in primary osteogenesis, we must first have provided a primitive connective tissue foundation. This arises in two ways: first, by the organization of the blood clot surrounding the injury, this being brought about by invasion of the clot with phagocytic cells of the blood and the eventual conversion of the clot into embryonic connective tissue; second, by the removal of the calcium from the bone at the point of injury, leaving only the connective tissue matrix. According to Leriche and Policard, this connective tissue matrix still further reverts to the embryonal stage in which calcium is most easily deposited.

In the repair of fractures, this necessary connective tissue matrix is probably formed in both ways, and calcium is then redeposited in a manner which will result in a continuous bone bridge across the injury and thus heal it. This cellular differentiation which takes place at the point of injury might seem to be a local factor, but is classed as a systemic one because it is brought about by the same general forces which underlie the differentiation of mesodermic cells in the embryo or the formation of granulation tissue wherever injuries occur in the body.

(*b*) *Calcium and Phosphorus Supply.*—When the necessary connective tissue matrix is present, the next essential for bone formation is an adequate amount of calcium and phosphorus in the blood stream. As previously stated, calcium is in constant demand for vital needs of metabolism. Until the general needs of the organism have been satisfied calcium will not be deposited in the bones, or if it has been deposited, it will be removed in response to such general demands. The body needs require the constant presence in the blood stream of from 9 to 11 mgm. of calcium per 100 c.c. of blood. To maintain this level, calcium must be supplied in the daily diet or else it will be taken out of the skeletal storehouse. It is well known in dietetics that the most common food deficiency is calcium. Most of the required food elements, including the vitamins, will be supplied by a general diet, but calcium will be lacking unless deliberate care is taken to supply it, or to see that the calcium-bearing portions of the foods we eat are not removed in preparing them for our tables.

(*c*) *Vitamin D.*—The effect of certain food deficiencies on bone growth has long been known. During the past few years it has become well established that vitamin D is a food element necessary for maintaining a supply of calcium for growing bones. It has also been fairly well established that this vitamin acts by promoting the absorption of calcium from the intestines. Unless the calcium taken in the food is absorbed into the blood, obviously it will be useless in the body metabolism. An ordinary liberal diet will usually supply sufficient vitamin D, provided there is also enough sunshine. In cases in which there is doubt about the sufficiency of this vitamin it can be artificially supplied.

(*d*) *Parathormone Action.*—The secretion of the parathyroid glands maintains the calcium level of the blood. The calcium taken in as food is used for this purpose if in sufficient amount and if absorbed into the blood; otherwise calcium will be removed from the bones by action of this secretion. It is a mistaken conception to think of parathormone as governing calcium deposition; the function of the secretion is to provide for the calcium needs of general metabolism by maintaining a constant supply in the serum and plasma; only when there is a surcharge of calcium in the blood is it stored in the bones. The action of this hormone, therefore, induces a flow of calcium from the bones into the blood stream, and an excess secretion (hyperparathyroidism) brings about either a general halisteresis, or localized decalcification in the form of bone cysts.

(*e*) *General Metabolic Factors.*—Other internal secretions also affect calcium deposition or calcium removal. The secretions of the thyroid, the pituitary, and the gonads all influence bone growth. The bone atrophy of hyperthyroidism is quite familiar. The decalcification of pregnancy and of lactation and the atrophy of old age are other illustrations of the influence of general factors on bone metabolism.

### LOCAL FACTORS

(*a*) *Local Blood Supply.*—Calcium is brought to and taken away from the bones through the blood stream. To maintain calcium equilibrium, therefore, it is necessary that the circulation through any given area of bone be stable. In fractures the injured surfaces are made ready for repair by removal of old calcium through the blood stream, and in the prepared connective tissue matrix fresh calcium brought by the blood stream is deposited. The cells which permeate the blood clot and

convert it into embryonic connective tissue are also brought by the blood stream. Any interruption of this blood supply will halt the process of osteogenesis or repair.

(*b*) *Cellular Activity.*—Probably the most disputed question in the study of osteogenesis concerns the nature and relative importance of the local cellular activity. This does not refer to the primary cellular differentiation which must precede any tissue formation, but the specific activity of bone-forming cells. The commonly accepted theory is that the osteoblasts make bone, either by depositing calcium through secretory activity of the cells, or, more indirectly, through the action of phosphatase secreted by these cells. Leriche and Policard do not agree with this theory, contending that both osteoblasts and osteoclasts are osteolytic, their function being to remove calcium and prepare the field for the chemical and mechanical deposition of new salts in such preformed connective tissue matrix, the osteoclasts according to their view being nothing more than hypertrophied and multinuclear osteoblasts. However, even according to this humoral theory of osteogenesis, the local cellular activity is essential because the resorption of the calcium in order to secure a primitive tissue matrix is a necessary precursor of any new bone formation. Therefore, whether we accept the humoral theory of Leriche and Policard, or the cellular theory of direct osteoblastic activity, upheld by Key and others, all are agreed that some form of cellular activity is essential and without it bone repair will not take place. Many experimenters have demonstrated that the osteoblastic cells of the periosteum (cambium, osteogenic, or proliferative layer of cells) are necessary for new bone production in the repair of bone defects. It is for this reason, perhaps more than any other, that approximation of bone fragments is essential and that bone production will not occur when the fragments are too widely separated. Infection destroys these cells, thus removing an essential element in repair and preventing bone development

(*c*) *Phosphatase Activity.*—The very interesting investigations started by Robison some years ago indicate that the calcium brought to the bone by the blood stream is broken up by an enzyme into forms which are more easily deposited. This enzyme he called phosphatase. It has never been definitely proved whether this enzyme is secreted by the osteoblasts and is, therefore, entirely a local factor, or whether it is supplied by other tissues and brought to the area through the blood stream. Robison believes it is a direct secretion of the osteoblasts and that this is their method of bringing about calcium depositin local areas. Certainly this explanation has the virtue of simplicity. In some cases of nonunion, there is evidence that osteoblastic and phosphatase activity is overdone. When the deposition of calcium in the ends of the broken fragments proceeds more rapidly than the organization of callus about the fracture, the process of repair defeats itself. Such rapid formation of dense bone could be due to hyperphosphatase activity.

(*d*) *Neurotrophic Control.*—In spite of much work on the subject, it is not yet quite certain just how osteogenesis and repair of bone are influenced by nerve control. We know that such a control does exist and that it is exercised through the sympathetic arc and probably by control of the circulation of the blood in bone tissue. It has been shown that increasing the rapidity of the circulation through bone tends to remove the mineral salts, and that vascular stasis promotes the deposition of calcium.

(*e*) *Mechanical Demands.*—The architecture of the bone is influenced by the mechanical demands thrown on it. To some extent the amount of calcium retained in bone is dependent on the stresses to which the bone is subjected. The fact that we have thinning of bone when it is placed at rest by splinting or by paralysis of muscles indicates that mechanical demands play an important part in bone development and possibly in bone repair. The importance of this factor may easily be over-emphasized, however. When a limb is placed in a splint

or becomes paralyzed and the bones decrease in density through removal of calcium, the effect must not all be ascribed to non-use, because other factors will have been altered, such as the nerve control and the blood supply. By manual massage of the muscles and maintenance of the vascular tone by heat and other measures, atrophy can be greatly retarded and may be entirely prevented.

With these systemic and local factors in mind, the bone conditions associated with the lack of a normal amount and distribution of calcium can be grouped according to the defect of metabolism which is responsible. Morse has given an excellent grouping which can be somewhat simplified.

(1) A failure in the primary cell differentiation in the mesoderm may result in defective development of the necessary connective tissue matrix for bone formation. When there is such a failure of mesoblastic cells to differentiate into the more highly specialized types of connective tissue, this defect is probably general throughout all body tissues, but is more easily observed in bones. Lacking the necessary connective tissue matrix, calcium and phosphorus cannot be laid down, even though they may be present in normal amounts or even in excess. We see this condition in osteogenesis imperfecta of infants and in fragilitas ossium of adults. It is utterly useless to attempt to remedy such a condition, because it is due to an hereditary tissue defect. Such bones will bend easily in early life and break just as easily in later life; fractures will usually promptly unite, showing that there is no lack of calcium supply or failure of other factors necessary for bone repair.

(2) *Bone Atrophy.*—The next group includes the different types of bone atrophy, or simple removal of a part of the calcium which has been deposited, in contradistinction to the loss of calcium through bone destruction or through alteration of the chemical condition of the blood. Willich recognizes five types of bone atrophy:

(*a*) *Nutritional or Starvation Atrophy, Due to Dietary Deficiency.*—Since the calcium level of the blood must be maintained, if the supply reaching the blood from the food is insufficient, the stored supply in the bones will be drawn upon, producing bone atrophy. The deficient calcium supply may result from several causes; insufficient intake in the food; improper diet so that the calcium, even when present in the food in adequate amount, will be precipitated in the intestine in an insoluble form and its absorption into the blood stream fail; insufficient vitamin D to promote the absorption of the calcium from the intestine into the blood; unusual metabolic demands which exhaust the calcium in the blood and call on the stored supply in the bones, unless such a condition is anticipated by properly regulated diet. Examples of nutritional atrophy will be found in infantile rickets, the halisteresis of pregnancy, and in malnutrition of any sort.

(*b*) *Disuse Atrophy.*—This is usually seen as a localized condition in which limbs are put at rest for fractures or in which paralysis has stopped muscular action. This type of atrophy demonstrates that use or mechanical stimulus is necessary for the preservation of developed bone structure. Bones apparently develop to a certain extent under the momentum of evolutionary and hereditary forces, and then assume shape and thickness in accordance with the mechanical demands thrown on them. The state to which they are brought by long continued non-use probably represents the condition they would have assumed had mechanical demands never been exerted on them.

(*c*) *Senile Atrophy.*—In advanced age the bones lose a good portion of their calcium and become more fragile as a result. This is probably due to a combination of defective nutrition and partial disuse.

(*d*) *Neurotrophic Atrophy.*—This is an infrequent condition and of interest in this discussion only as a demonstration that neurotrophic influence is necessary to maintain the integrity of bone tissue. Smith has recorded the appearance of neuro-

trophic osseous atrophy in three generations of the same family. The condition is perhaps more familiar to us in the bone changes seen in leprosy, syringomyelia, and sometimes in tabes dorsalis, in the bones of the feet and hands.

(*e*) *Acute Reflex Atrophy.*—Originally described by Südeck and best known by his name, it has been variously called acute painful atrophy, acute painful osteoporosis, painful osteomalacia, acute trophic atrophy, acute circulatory atrophy. In this type there occurs an irregular removal of the calcium, apparently through circulatory changes in the bone structure induced by reflex stimuli travelling over the sympathetic nerves.

(3) *Endocrine Defects.*—The deposit of calcium in bone and its removal to meet general metabolic demands will be influenced by any internal secretion which is concerned with the rate of metabolism. The thyroid gland, which exercises control over the general rate of metabolism through its influence on oxidation, includes bone tissue in its field of influence. Hyperthyroidism will bring about a removal of calcium from the skeleton in order to meet the increased demands of general metabolism. Diabetes mellitus and certain pituitary conditions, through alteration of the amount of their secretions, will break the orderly cycle of metabolism and influence the amount of calcium deposited in the bones.

The specific internal secretion which has direct control over the rapid mobilization of the calcium stored in the bones is parathormone, which is secreted by the parathyroid glands. Apparently it is through this secretion, broadcast by way of the circulation, that the demand of general metabolism for calcium is conveyed to the bones, this demand being met by flow of calcium from the bones into the circulation. An excess of parathyroid secretion results in a corresponding excess removal of calcium from the bones (halisteresis). When calcium appears in the blood stream in response to such a pathologic stimulus, and there is no real need for it, it may be redeposited in an irregular manner almost anywhere in the body. In hyperparathyroidism, therefore, we may have a generalized halisteresis or localized areas of calcium loss in the bones (cysts), and in addition there may be irregular and undesirable deposits of calcium in other portions of the same bone from which it has been removed, or in bones elsewhere in the body. It may be deposited in the connective tissue structures in or about the joints, such as cartilages, ligaments or tendons; it may deposit as calculi in the urinary tract; it may deposit in the connective tissue of blood vessels, in the muscles, in hematomas, in gland structures, or anywhere in the body where connective matrix is present and where the other necessary systemic and local factors converge to produce bone.

(4) *Disease Metabolism.*—There are some conditions associated with changes in the chemical condition of the blood which cause the calcium to be dissolved out of the bones. One of the most striking of these is the halisteresis of chronic arteriolar nephritis, the so-called "renal rickets." This is probably due to the inability of the kidneys to excrete phosphorus which accumulates in the blood, and must be rendered inert by combination with other salts; calcium is the most available element and is removed from the bones for this purpose. Renal rickets produces the most marked halisteresis found in any condition. Probably the decalcification which occurs at menopause and the atrophy of old age are associated with altered chemical conditions of the blood.

(5) *Specific Bone Diseases.*—Such diseases as bone infections, Schüller-Christian's disease, Niemann-Pick's disease, Paget's disease, Hodgkin's disease of bone, multiple myeloma or the osteoclastic malignancies, whether primary or metastatic, are local conditions and not essentially metabolic, and are not, therefore, considered in this paper.

## DISCUSSION

It will be more in accord with present-day physiology to look on the skeleton as

a battleground of contending metabolic forces and to direct attention as much to those forces as to the bones themselves, when dealing with injuries. In rickets we bring about the necessary change in bone development by attention to systemic factors. In diffuse cystic osteitis, a reversal of the flow of calcium is produced by removal of the parathyroids or inhibition of their action by radiation.

In industrial injuries to bones it is necessary to pay attention to the systemic factors as well as to the local factors, if we are to secure normal and speedy repair of the injury. As illustrations of this necessity, two types of bone lesions will be briefly mentioned.

In acute reflex atrophy (Südeck's), the changes in the bones are local and due to disturbances of the sympathetic nerve control—a local factor. The treatment of this condition is based on maintenance of the circulation at a normal rate through the involved area and prevention of stasis and edema. This is done by heat, massage, and passive motion, avoiding splints and casts. At the same time, the systemic factors should not be neglected, because the process of recovery is a long one and during this time all the systemic and local factors necessary for bone repair should be maintained at optimum efficiency.

No doubt there are many patients who have excess parathyroid secretion and in whom there is a tendency for calcium to flow out of the bones; such patients may have a generalized halisteresis without bone cyst formation. Such patients are not only more subject to bone injury, but their bone repair is rendered difficult because of this tendency to withdraw calcium instead of depositing it. Moffat has written on pathologic fractures of the spine associated with calcium metabolism; he believes that the condition is due to a faulty diet and can be diagnosed by its x-ray appearance. Ballin gives five types of parathyroid disorder, one of which—the vertebral type—is important from the industrial standpoint. Pemberton and Geddie include among the clinical features of hyperparathyroidism, rarefaction of bones with or without cyst formation, hypotonia, and muscular weakness. Bauer gives among the symptoms due to alteration of calcium and phosphorus metabolism, weakness and loss of strength, muscle and joint pains, bone tenderness, and frequent fractures from slight trauma. These symptoms have a familiar sound to the industrial surgeon who handles back injuries, and should suggest that less concentration of attention on braces, plaster casts, and adhesive taping and more consideration given to proper diet, sunshine, and vitamin D might hasten recovery in many of these cases.

Illustrations could be multiplied but the purpose of this paper is a general one, to emphasize the importance of a broader conception of injuries to bones, based on a knowledge of calcium metabolism, rather than a discussion of specific cases.

# TREATMENT OF FEMALE ENDOCRINOPATHIES[1]

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THE endocrine glands have, since first discovered, offered a very perplexing problem to the clinician both in diagnosis and therapy. Rapid strides have been made in the understanding of the function of the various glands and their interaction, but this is far from complete. Knowledge of the glands which control the female sex function is perhaps more advanced than in any other field of endocrinology and many of the functional disorders of the female are recognized as glandular in origin. But the mechanism of this complex function has not been sufficiently demonstrated so as to serve as a basis of specific therapy. The identity and individuality of some of the hormones have not been determined, and in many cases it has not been proven which hormones cause certain reactions. Also, endocrine disorders are not the result of the lack of or the over-abundance of a single hormone with complete normalcy of the other glands. The abnormal function of one gland is usually accompanied by decreased function in some of the other glands of the endocrine system, with compensatory hyperactivity of still others, depending upon the normal interaction of the glands.

For these reasons organotherapy is not sufficient in treating functional disorders of the female, though we have some of the hormones in pure form and in potent concentration. We have, therefore, sought some other means of treating the cases which might more nearly relieve the cause of the disorder than glandular products which are purely substitutional in action. We refer to irradiation of the pituitary gland.

This method of treatment is not very recent; however, it has been used more extensively in Europe than in this country. It was introduced by Hofbauer (1), in 1922, before the German Gynecological Congress. Rubin (2, 3), in 1926, and Kaplan (4) reported the use of x-ray therapy to the ovaries and to the pituitary gland in cases of amenorrhea and functional sterility. Ford (6) and Drips (5), in 1928, and Collins *et al.* (7), in 1936, found irradiation helpful in relieving the symptoms associated with the menopause. Recently (1935), Newell and Pettit (8) reported excellent results in cases of functional dysmenorrhea treated with pituitary irradiation. Mazer and Spitz (9), in 1935, found irradiation helpful in the functional menstrual disorders.

In using x-ray to the pituitary gland we make no pretense of explaining its method of action. We have found that it is effective, which must be sufficient for the time being: no one as yet really knows how it works. This is attested to by the fact that there is such a wide divergence of opinion as to its *modus operandi.* Some able clinicians say that all x-ray is destructive, hence irradiation can be beneficial only when there is a state of hyperfunction, and reduction of the activity of the gland is indicated. Others base their opinion of the action upon the hypothesis that every action is accompanied by a counteraction and that in this case irradiation causes a depression which is followed by recovery of function, which may proceed to a greater activity than was formerly present, provided that depression has not been pushed to the point of complete destruction. There are still others who maintain that x-ray in small doses is stimulating or causes a hyperemia which results in stimulation of the gland. Without holding to any theory as to the mechanism of its action, we specify stimulating doses of

[1] Presented before the Fifth International Congress of Radiology in Chicago, Sept. 13–17, 1937.

x-ray because we feel that the end-results are those of stimulation.

Since we use irradiation of the pituitary gland in many of the functional disorders of the female, the question naturally arises as to how one method of treatment can be effective for so many different clinical entities. In answering this, two aspects of the problem must be considered: First, we believe that the causes of most of the functional disorders of the female differ from each other more in degree than in kind, that the degree of disturbance of the ratio of the female sex hormones is the important factor in determining the clinical manifestation of that disturbance; second, the pituitary is the master gland of all endocrines. The ovary is completely under its dominance. Most of the functional disorders are not primary in the ovary but are the result of improper pituitary action. It may be asked how irradiation can affect one of the functions without affecting the others. In answer, it seems impossible for a gland of such simple histologic structure to have so many independent actions; that in cases in which there is a disturbance in one function there is probably disturbance in more. When we have adequate clinical tests for these functions this problem will be clarified.

What cases are suitable for irradiation? First of all, it should be stressed that all cases to be treated for a functional disorder should be thoroughly studied to ascertain whether there is present any pathology, local or systemic, before endocrine therapy is administered. The endocrines are, after all, only a part of the whole and as such are subject to depressant action the same as other organs. It is well known that foci of infection, anemia, psychic and emotional disturbances, etc., can affect specific functions of the body, such as cardiac action. In like manner, such factors can affect the endocrine glands. When such factors have been definitely and conclusively excluded as etiological factors, then and only then can any form of endocrine therapy be administered with any hope of success. We stress these very obvious facts because they are the most important factors in successful endocrine therapy. Though they seem obvious, they have been neglected and endocrine therapy used. When results were not forthcoming endocrine therapy has been branded as worthless. The discredit thus placed on this form of treatment is both unjust and unfair.

After the case has been established as endocrinal in origin there is no contraindication to irradiation therapy in the small doses advocated. With these minimal doses there are no unpleasant secondary reactions other than occasional nausea or headache for a few hours. When irradiation was first used larger doses were employed and epilation occurred, but this is absent with the present dosage. X-ray used in small doses has no deleterious effects on subsequent pregnancies. Its use need not be confined to any particular age group.

We have not used irradiation exclusively and do not advocate such usage. In conditions in which organotherapy is indicated and potent products are available, we used them. We have used organotherapy alone and feel that the results thus obtained are not so good or so lasting as those obtained by organotherapy and irradiation combined.

## AMENORRHEA

Amenorrhea is perhaps the most profound type of ovarian failure. Hormone studies of amenorrheic women usually reveal a deficiency of the estrogenic substance, the amount varying with the degree of ovarian failure. Rarely an excessive amount is found in the blood, which is attributed not to excessive production but to faulty elimination, since the urine level is usually low. The uterine scrapings almost invariably show ovarian failure, the picture which was formerly called "atrophic endometritis." Scanty and irregular menstruation indicates ovarian failure, which differs from that of complete amenorrhea only in degree.

Based on this concept of amenorrhea, what would be the logical method of therapy? If the deficiency lies in the

thyroid, the problem is comparatively simple and results are good; but if the fault lies in the gonads or the pituitary, it becomes considerably more difficult. We know that we can produce uterine bleeding, even typical progestational endometrium, by the administration of large doses of theelin and progestin, but such a procedure will have to be repeated for each menstrual period—an expensive procedure and one of which the patient will soon tire. Furthermore, what is to be gained by it? Amenorrhea in itself is harmless. It is the underlying cause which should be corrected. There is only one justification for using ovarian hormones in amenorrhea and that is to convert an infantile, unresponsive uterus to that of the adult type. Can we stimulate the ovaries or pituitary? At the present time, we do not have available for therapeutic use a product containing the follicle-stimulating factor of the anterior pituitary gland, which has been proven to be effective clinically. The gonadotropic substance of pregnancy urine is essentially luteinizing in character and this effect is not very marked in the human. Our one hope, at the present, of restoring the normal function of the ovary or pituitary is by irradiation of the pituitary gland. This we have used with the results as tabulated in Charts I and II.

CHART I.—AMENORRHEA

| No. | Types | | | Treatments | | | | | Results | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Normal | Infant. | Obese | X-ray | Thyroid | Prog.-B | Ant.-S | Proluton | Relieved | Improved | Failure |
| 22 | 12 | 5 | 5 | 22 | 10 | 8 | 1 | 2 | 16 | 5 | 1 |

Typical Cases

| Case | Age | Duration of Amenorrhea | Other Symptoms | Laboratory | Treatment | Results |
|---|---|---|---|---|---|---|
| C. C. | 15 | Never menstruated | Obesity | B.M.R.-13 | Diet<br>X-ray<br>Thyroid | Periods q. 28 days |
| L. L. | 27 | 10 months | Obesity | B.M.R. + 2<br>Pit.-neg.<br>Estrin-neg. | Diet<br>X-ray<br>Thyroid | Started menstruating 1 mo. after x-ray; now regular |
| L. K. | 34 | 3 years | Infantile | . . . | X-ray<br>Ant.-S<br>Thyroid | Regular q. 28 days |

CHART II.—OLIGOMENORRHEA—HYPOMENORRHEA

| No. | Treatments | | | | | Results | | |
|---|---|---|---|---|---|---|---|---|
| | X-ray | Thyroid | Progynon-B | Ant.-S | Proluton | Relieved | Improved | Failed |
| 20 | 20 | 7 | 9 | 4 | 2 | 13 | 7 | 0 |

Typical Cases

| Case | Age | Menstruation | Laboratory | Treatment | Results |
|---|---|---|---|---|---|
| H. D. | 27 | 15–5–28<br>scant | Estrin-neg.<br>Pituitary-neg. | X-ray-3 | Periods normal amount |
| L. M. | 34 | q. 6–8 mo. | B.M.R. − 10<br>Estrin very weak<br>Pituitary-neg. | X-ray | Periods q. 28 days; became pregnant |
| C. R. | 31 | 13–$^1/_2$–28 | Pituitary-neg.<br>Estrin-weak | X-ray<br>Thyroid<br>Proluton<br>Progynon-B | Periods normal in amount |

### FUNCTIONAL BLEEDING

The etiology of functional bleeding, which includes menorrhagia and metrorrhagia, is unknown. However, we have found that in most cases uterine scrapings reveal over-stimulation of the endometrium by the follicular hormone with decreased or absent luteal activity. The cases usually respond exceptionally well to the use of the gonadotropic hormone or the corpus luteum hormone. In difficult and resistant cases, irradiation of the pituitary is helpful, as shown in Chart III.

### DYSMENORRHEA

The etiology of functional dysmenorrhea has long been a moot question. Studies by methods which are only recently available—blood and urine hormone tests and endometrial biopsy—seem to indicate that there is a disbalance of the two ovarian hormones with a relative excess of theelin. This represents a type of ovarian failure which is usually due to insufficient stimulation of the ovary by the anterior pituitary. Treatment is directed, therefore, toward the restoration of the normal ratio

CHART III.—FUNCTIONAL BLEEDING

| | | Treatments | | | Results | |
|---|---|---|---|---|---|---|
| No. | Frequency of Bleeding | X-ray | Ant.-S | Thyroid | Relieved | Failure |
| 8 | Continuous to 21 days | 8 | 4 | 3 | 6 | 2 |

Typical Cases

| Case | Age | Menstruation | Laboratory | Treatments | Results |
|---|---|---|---|---|---|
| M. B. | 23 | q. 14–20 days lasts 5–60 days | B.M.R. – 10 | X-ray Ant.-S Lextron | Normal periods for last 10 months |
| S. P. | 21 | Continuous for 60 days | B.M.R. – 12 Hypertrophic-endometrium Estrin-positive | Splenic ray 1 X-ray Pit.-2 Pelvic Ray Proluton Thyroid Ant.-S | No results until 1,750 mg. radium in cervix |
| F. F. | 44 | q. 28 days lasts 14 days; clots | Uterine scraping; Mycotic infection | X-ray Ant.-S | Slight improvement |

CHART IV.—DYSMENORRHEA

| No. | Treatments | | | | Results | | |
|---|---|---|---|---|---|---|---|
| | X-ray | Ant.-S | Proluton | Thyroid | Relieved | Improved | Failure |
| 33 | 33 | 21 | 7 | 29 | 29 | 4 | 0 |

Typical Cases

| Case | Age | Duration of Symptoms | Other Endocrine Stigmata | Treatments | Results |
|---|---|---|---|---|---|
| M. F. | 27 | 4 years | Sterility | Irradiation Proluton Thyroid | Relieved |
| D. H. | 24 | 10 years | Infantile uterus B.M.R. – 21 | Irradiation Thyroid Ant.-S | Relieved |
| H. D. | 32 | 12 years | Infantile build | Irradiation Proluton | Relieved |

of the two hormones. Irradiation of the pituitary gland supplemented by administration of the corpus luteum hormone gives excellent results, as shown in Chart IV.

### MENOPAUSE

The menopause syndrome is an endocrinopathy of polyglandular origin, the primary factor of which is loss of ovarian function. This is followed by a compensatory hyperfunction of the anterior pituitary gland. Other glands, as the thyroid and adrenals, are also contributory factors of more or less importance. It has been demonstrated that at the time of the menopause there is a progressive decrease of the theelin in the blood and urine, accompanied by a progressive increase in the amount of the pituitary gonadotropic hormone. Furthermore, that the subjective symptoms, as hot flashes, are due to the presence of this excessive amount of pituitary hormone. Therefore, treatment, which seeks only to control the unpleasant symptoms, should be directed toward reduction of this excess. This can be accomplished by administration of theelin and by irradiation. The severity and duration of the symptoms will determine the mode of therapy. In mild cases, organotherapy is usually sufficient. In the more severe cases, the addition of irradiation of the pituitary gives better results than organotherapy. Results are tabulated in Chart V.

### STERILITY

Functional sterility may occur as an accompaniment of some menstrual disorder or it may occur in an apparently normal woman with a regular menstrual cycle. The findings in the former are sufficient to explain the sterility. In the latter, the clue to the situation is found in the study of the endometrium, for which purpose a small amount of tissue is taken and examined microscopically. Normally the endometrium undergoes a cyclic change which is governed by the cyclic changes in the ovaries and from both an anatomical and physiological standpoint can be divided into two corresponding phases—the follicular and the luteal. In many of the cases of sterility we have found evidence

CHART V.—MENOPAUSE

| No. | Treatments | | | Results | | |
|---|---|---|---|---|---|---|
| | X-ray | Thyroid | Progynon | Relieved | Improved | Failed |
| 20 | 20 | 3 | 17 | 13 | 6 | 1 |

Typical Cases

| Case | Age | Mense. | Preg. | L.M.P. | Meno. Symptoms | Other Symptoms | Treatment | Results |
|---|---|---|---|---|---|---|---|---|
| McP. | 53 | 13–6–28 | 4 | 20 yrs. before | Nervousness; occasional flash | Periodic rhinitis | X-ray | Relief for 15 mo. of nervousness and rhinitis |
| G. D. | 43 | 12–4–28 | 2 | Still menstruating | Flashes Headaches | Obesity | Progynon-B Thyroid X-ray Diet | Symptoms relieved; loss of 15 lb. |
| E. C. | 50 | 3–5–28 | 5 | 1–7–35 | Flashes Depression Nervousness | Obesity | Progynon-B q. 4 days for 3 mo. X-ray Pit. Tonic | Relief of all symptoms |
| I. R. | 40 | ... | 3 | 1934 | Extremely nervous, felt as though were going crazy | ... | X-ray Pit. Progynon-B | Cured of symptoms |

of two types of ovarian failure—failure of corpus luteum formation which results in incomplete progestational changes in the endometrium or low degree of luteal differentiation, and failure of ovulation. It is now an accepted fact that menstruation can and does occur without ovulation. This phenomenon can be diagnosed by study of the endometrium which shows no evidence of progestational changes whatsoever. These anovulatory cycles are absolutely sterile cycles.

The cause of this ovarian hypofunction may be primary in either the pituitary or the ovary. The pituitary may not secrete sufficient amount of the gonadotropic hormones to carry the ovary through its complete cycle. If this is the case, x-ray therapy to the pituitary is used. The ovary may contain many follicular or corpus luteum cysts which prevent ovulation. Here x-ray directly to the ovary is indicated. With x-ray therapy the corpus luteum hormone, progesterone, is also used to insure complete progestational proliferation of the endometrium.

There are some cases, however, which have still another contributory factor, low thyroid function; until this deficiency is corrected, they do not conceive. Results are recorded in Chart VI.

Spontaneous abortion may be considered as a type of sterility for, though the patient conceives, she is unable to carry the pregnancy to a successful conclusion. Exclusive of non-endocrine cases, the basis of this condition is also corpus luteum failure. The luteal hormone not only prepares the endometrium for reception of the ovum but, after fertilization and nidation

CHART VI.—STERILITY

| No. | Years Sterile | Other Endocrine Stigmata | | | Treatments | | | | | | Results | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Obese | Amen. | Infant. | X-ray | Diet | Thyroid | Theelin | Ant.-S | Prol. | Pregnant | Failure |
| 11 | 11 | 8 | 2 | 2 | 11 | 8 | 9 | 5 | 2 | 1 | 10 | 1 |

Typical Cases

| Case | Years of Sterility | Age | Previous Pregnancies | Other Symptoms | Treatment | Results |
|---|---|---|---|---|---|---|
| H. D. | 20 | 38 | 0 | Headaches | X-ray Post. Pit. | Delivered by caesarean section |
| S. D. | 10 | 39 | 2 | Obesity; headaches | X-ray Thyroid Post. Pit. Diet | Twins |
| S. S. | 3 | 30 | 0 | Obesity | X-ray Thyroid Progynon-B Diet | Pregnant 1934 and 1936 |

CHART VII.—SUMMARY OF RESULTS

| | No. | Relieved | Improved | Failure |
|---|---|---|---|---|
| Amenorrhea | 22 | 16 | 5 | 1 |
| Oligomenorrhea and Hypomenorrhea | 20 | 13 | 7 | 0 |
| Functional Bleeding | 8 | 6 | 0 | 2 |
| Dysmenorrhea | 33 | 29 | 4 | 0 |
| Menopause | 20 | 13 | 6 | 1 |
| Sterility | 11 | 10 | 0 | 1 |
| Total | 114 | 87 | 22 | 5 |
| Percentage | | 76.3 | 19.3 | 4.4 |

of the ovum have occurred, it serves to maintain pregnancy. If it is present in insufficient quantity, loss of fetus ensues. This type of abortion can be prevented by adequate administration of progesterone.

### OBESITY

Obesity is not a clinical entity, but is a symptom which may be due to many causes. From an endocrine standpoint, it is most often due to pituitary, thyroid, or ovarian failure, singly or combined. Each case must be studied individually and treated accordingly. In the treatment of any type of obesity, diet is of first importance. Thyroid extract is helpful in most cases, but cases are encountered whose weight-reduction cannot be affected by diet or diet and thyroid. The addition of irradiation to the therapy facilitates reduction considerably.

### SUMMARY

1. It is believed that the causes of most of the functional disorders of the female differ from each other more in degree than in kind and that the degree of disturbance of the ratio of the female sex hormones is the important factor in determining the clinical manifestations of that disturbance.

2. Most of the functional disorders are not primary in the ovary but are the result of improper pituitary action.

3. Knowledge of the physiology and chemistry of the female sex function is not complete enough to serve as a basis for specific organotherapy in disturbances of this function.

4. The combination of irradiation of the pituitary gland with appropriate hormone preparations, when they are available, is the most effective method of therapy in functional disorders of the female which we have available at the present time.

5. Various types of female endocrinopathies numbering 115 cases have been treated by combination of irradiation of the pituitary gland and organotherapy, of which 87 (76.3 per cent) were relieved, 22 (19.3 per cent) improved, and five (4.4 per cent) were failures.

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# STUDIES ON THE EFFECT OF RADIATION UPON GROWTH AND RESPIRATION OF VARIOUS TISSUES *IN VITRO*

## THE LETHAL DOSE AND THE SUBLETHAL DOSE OF X-RAYS AND RADIUM: PRELIMINARY REPORT[1]

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IN spite of the extensive literature on the effect of radiation on living matter, there is no definite knowledge regarding the biological response of various tissues to different sources of radiation or the dose required to inhibit the proliferation of living cells, particularly malignant cells. Even such basic factors as the lethal dose and the sublethal dose for various types of tissues, particularly mammalian, have not been definitely determined.

In attempting to fix stable conditions for the determination of these factors the following criteria, more or less arbitrary, have been selected: (1) To determine the amount of radiation which will inhibit the growth of an explant during 48 hours' incubation following radiation. This will be termed the lethal dose. (2) The highest amount of radiation which would just permit a slight proliferation of the explant to take place. This will be called the sublethal dose.

Instead of newgrowths *in vitro* which have been subcultured several times, as used by other investigators, we have irradiated explants of freshly excised tissues as well as new active growth in primary or original cultures. A brief explanation for this use of only fresh explants and primary growth in cultures is necessary. In some quarters the objection is advanced that subcultures of several passages do not possess the same qualities as body cells. In using fresh explants and primary growth in cultures this objection is overcome, although the lack of a blood supply has not been remedied.

The sources of normal mammalian fibroblasts and epithelial cells of embryonic origin were the heart, kidney, and tongue removed under aseptic precautions from two- to three-month-old human embryos and the heart and kidneys of one- to two-day-old rats. Explants of the heart from seven- to eight-day-old chick embryos, producing always 100 per cent growth *in vitro*, were used as an index for these experiments.

Explants in freshly made cultures were exposed to radiation of x-rays, radium, and radon. The dose was gradually increased until no growth of new cells from the explant took place following 48 hours of incubation after irradiation. As neoplastic tissues, human myxosarcoma of the thigh, and Mouse Sarcoma 180 were used. In order to investigate the effect of radiation on actively growing cells, primary or original cultures were used. Only those doses which were found to be sublethal or lethal for the explants were employed here.

### EXPERIMENT WITH X-RAYS

A half wave valve tube generator and a thin-walled Coolidge tube were used as the source of x-rays. The cultures were irradiated at a focal distance of 40 cm., using 200 kv. at 6 ma. with 1 mm. aluminum filter (effective wave length of 0.32 Å.). Under these conditions 80.75 r/min. was the average intensity measured in air without back-scattering. The temperature in the area of the cultures was between 30 and 35° C. during radiation.

[1] Presented before the Fifth International Congress of Radiology in Chicago, Sept. 13–17, 1937.

Under these conditions explants of the above-mentioned tissues were irradiated with doses ranging from 3,000 to 30,000 roentgens. Only the results obtained with high doses of x-ray will be reported here.

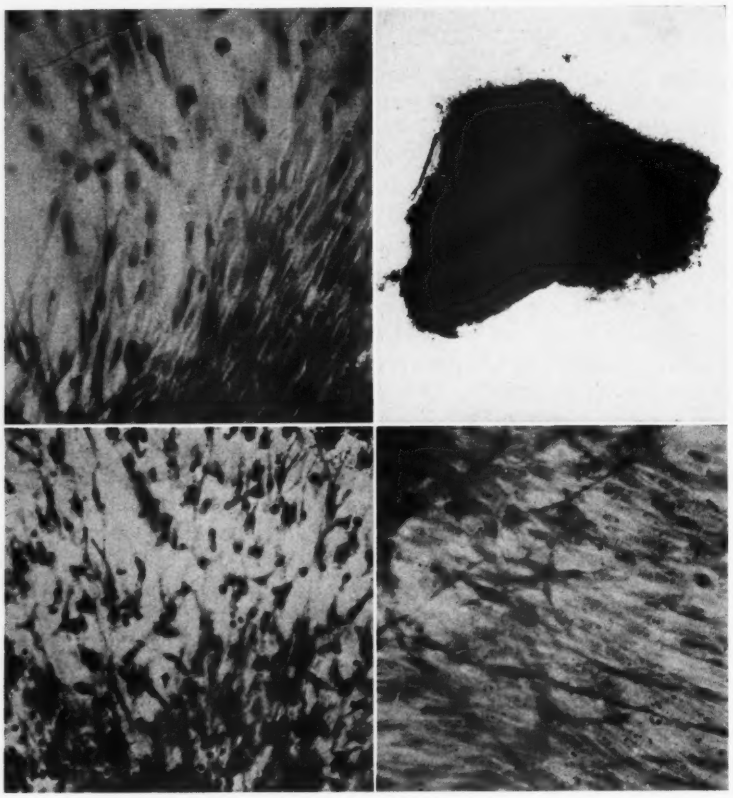

Fig. 1. An explant of embryo chick heart irradiated with 20,000 r. The growth shown in the illustration occurred during 48 hours' incubation following irradiation. The cells appear to be normal. (*Upper left.*)

Fig. 2. An explant of embryo chick heart irradiated with 30,000 r. No growth or outwandering cells are present. (*Upper right.*)

Fig. 3. A 24-hour growth *in vitro* of embryo chick heart irradiated with 30,000 r and observed 48 hours after radiation. As can be seen, the cells are degenerated, the offshoots from the fibroblasts are in most instances broken up, the protoplasm shrivelled, and the nucleus elongated or broken up. (*Lower left.*)

Fig. 4. A 24-hour growth *in vitro* of embryo chick heart as a control to Figure 3. Note the normal appearance of the cells. (*Lower right.*)

When explants of the above-mentioned tissues were irradiated with 30,000 r no growth or outwandering cells occurred in the cultures during 48 hours' incubation, while explants exposed to 20,000 r showed a fair growth during the following 48 hours' incubation. This newgrowth, however, was smaller in size than that of the control cultures. Fat droplets were also present in this culture which is a sign of early degeneration. When explants were exposed to 25,000 r just a few outwandering cells could be observed in some of the cultures during 48 hours' incubation.

Actively growing cells of fibroblasts in primary or original cultures of the above-mentioned tissues as well as of human myxosarcoma and Mouse Sarcoma 180 degenerated after they were exposed to radia-

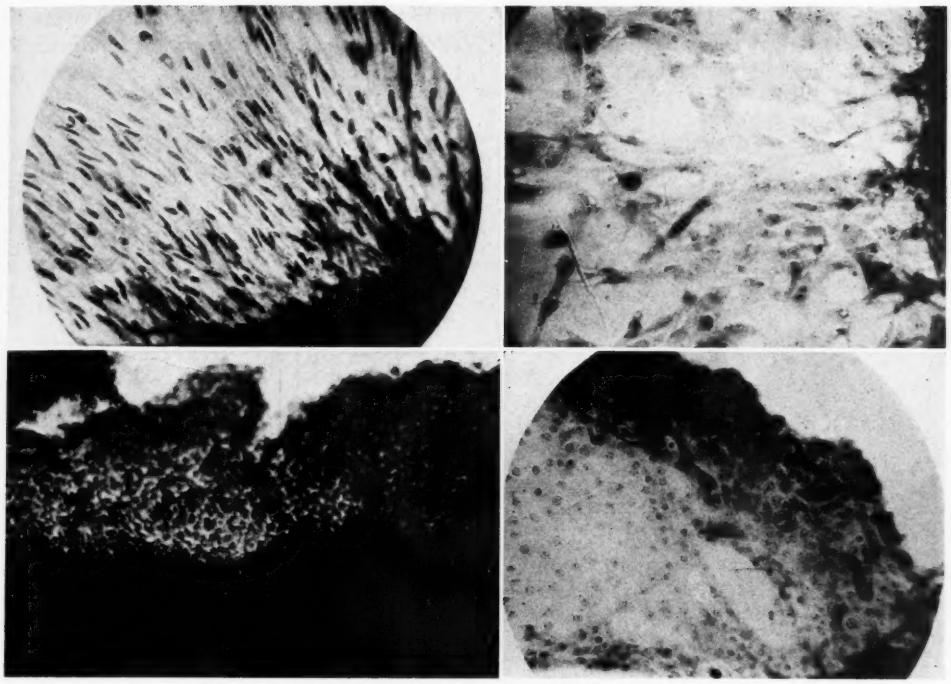

Fig. 5. A culture with an active growth of human myxosarcoma irradiated with 30,000 r and observed 48 hours later. The illustration shows degenerated cells, the nucleus elongated and in some instances broken up and the protoplasm shrivelled. (*Upper left.*)

Fig. 6. A culture of human myxosarcoma as control to Figure 5. Note the different appearance of the cells. (*Upper right.*)

Fig. 7. An explant from the tongue of a $3^1/_2$-month-old human embryo irradiated with 30,000 r. Note a slight dense growth of epithelial cells which occurred during 48 hours' incubation following irradiation. (*Lower left.*)

Fig. 8. An explant from the kidney of a one-day-old rat irradiated with 30,000 r. Note the small growth of epithelial cells which occurred during 48 hours' incubation following irradiation. (*Lower right.*)

tion of 30,000 r. The offshoots of the fibroblasts were broken up, the protoplasm shrivelled, and the nucleus in many instances elongated or was broken up (karyolysis). The photomicrographs (Figs. 1, 2, 3, 4, 5, and 6) demonstrate the results of this experiment. On the basis of the observations made, it can be concluded that 20,000 r is a sublethal dose for the proliferation of the above-mentioned tissues, while the dose of 30,000 r can be regarded as a lethal dose for explants as well as for actively growing fibroblasts of the same tissues. (It should be mentioned that the total dose of x-rays was administered in a single treatment, not in fractionated doses.)

Different observations were made when cultures of the tongue and kidneys from human embryos and from kidneys of young rats and mice were exposed to 25,000 and 30,000 r. A slight growth of epithelial cells occurred in some of the cultures during 48 hours' incubation after irradiation, but there was no growth of fibroblasts. (Figures 7 and 8 demonstrate this phenomenon.) The same observations were made on several repeated experiments. While a growth of mixed cells, fibroblasts, and epithelial, occurred in the control cultures (see Fig. 9), only a small growth of epithelial cells took place in the explants which received 25,000 or 30,000 r. When cultures of the kidneys with an active growth of mixed cells, fibroblasts, and epithelial cells were exposed to 30,000 r and watched during 24 hours' incubation

following radiation, the fibroblasts appeared to be degenerated while the epithelial cells apparently seemed not to be damaged. It can be assumed, therefore, that the fibroblasts are more sensitive to a given dose of radiation than the epithelial cells. Further experiments are in progress in order to reach a more definite conclusion on this point.

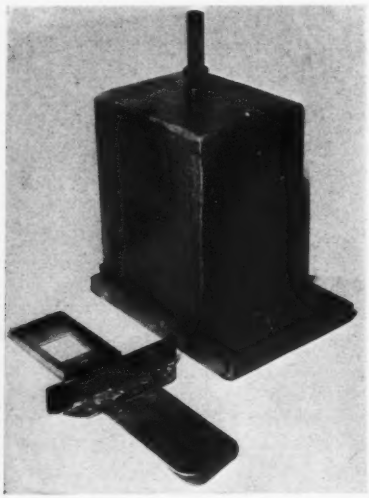

Fig. A. Lead chamber.

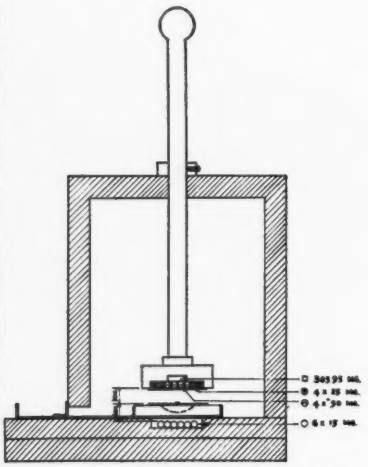

Fig. B. Geometrical arrangement of 693.93 mg. radium.

### EXPERIMENT WITH GAMMA RADIATION

For the experiment with radium a lead chamber was constructed as shown in Figure *A*. The glass slide with the culture was placed on a tray and inserted through the lower opening into the lead chamber (see Fig. *A*). The radium element consisted of:

| | | |
|---|---|---|
| 4 radium tubes of 50 mg. each = 200<br>4 radium tubes of 25 mg. each = 100<br>6 radium tubes of 15 mg. each = 90 | | 0.5 mm. platinum filter |
| and a radium capsule of | 303.93 | 0.5 mm. silver filter |

The radium tubes were placed side by side in a holder so that the radiation would be as uniform as possible. Figure *B* shows the geometrical arrangement of the radium elements. As can be seen, some of the radium tubes were placed beneath the culture, but the major part was above the culture at 1.0 cm. distance in both instances. Attention should be called to the fact that this experimental set-up was far from ideal. An ideal arrangement would have been to have all the radium element in one capsule. This, however, was not available.

As computed by C. B. Braestrup, our physicist, the radiation from the 693.93 mg. radium element is equivalent at the center of the culture to that from a point source of approximately 270.0 mg. at 1.0 cm. distance and 0.5 mm. platinum filter.

The radiation of the culture took place in an incubator at 37.5° C., separate from the control cultures. Explants were irradiated immediately after they were placed in the culture medium. This was done in order to determine under what amount of radiation the tissue could proliferate. When an effective dose of gamma radiation was determined on explants this dose was later given to cultures with active growth of new cells in order to study its effect on proliferating cells. The amount

of radium element as well as the time of exposure was increased until a lethal dose for explants of the previously mentioned tissues was reached. Only the results obtained with an effective dose of gamma radiation are reported here.

When explants of embryo chick heart and of heart from one- to two-day-old rats were exposed to radiation of 390 mg. radium element (1.0 cm. distance, 0.5 mm. platinum filter), newgrowth of fibroblasts was observed during 18 hours' exposure. This growth, however, was smaller than that of the control cultures. When this culture was left for another 18 hours under radiation, no further growth occurred. The newgrowth from the previous day did not have a healthy appearance, and many fatty droplets were present in the culture, a sign of early degeneration. When explants of the same type of tissue were exposed to radiation of 693.93 mg. radium element for 19 hours, no growth at all from the explant took place. The cultures did not recover, *i.e.*, no growth occurred from the irradiated explants during 48 hours' incubation. In order to find the sublethal dose, explants were exposed to the same amount of radium element for 2, 4, 7, 9, and 13 hours. A good growth of new cells was observed in the cultures which were irradiated for 2, 4, 7, and 9 hours after 18 hours' incubation. Even the pulsation of the heart fragments could be seen in some of these cultures. Explants exposed to radiation for 13 hours showed a very small growth of fibroblasts and some outwandering cells were scattered in the field after 48 hours' incubation following irradiation. It was further noted that a culture of embryo chick heart with an active starting growth

Fig. 9. A culture from the tongue of the same human embryo as that shown in Figure 7. Note a normal growth of mixed cells, epithelial cells, and fibroblasts.

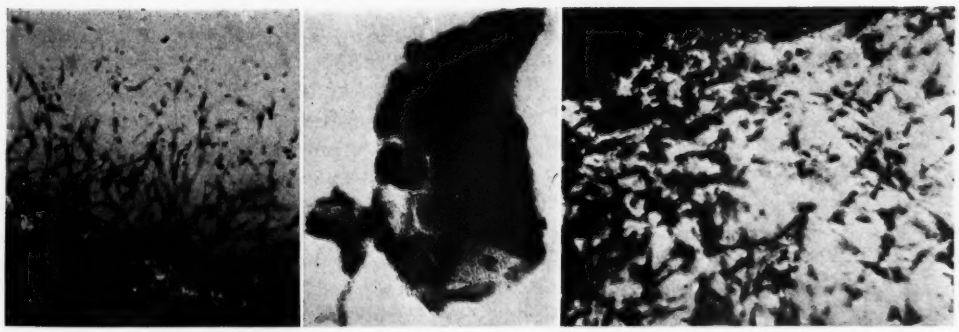

Fig. 10. An explant of embryo chick heart exposed to radiation of 693.93 mg. radium. Note the growth of fibroblasts which occurred during 13 hours' radiation at 37.5° C. This growth was smaller and thinner than that of the control cultures. The culture received 9,022 mg.-hours. (*Left.*)

Fig. 11. An explant of embryo chick heart exposed to radiation of 693.93 mg. radium during 19 hours. Note that there is no growth or any outwandering cells. Culture received 13,186 mg.-hours. (*Center.*)

Fig. 12. A culture of rat heart with an active growth of fibroblasts was exposed to radiation of 693.93 mg. radium for 19 hours, receiving 13,186 mg.-hours. Note the destroyed cells. Offshoots of the fibroblasts were broken up, the protoplasm shrivelled, and the nucleus in most instances vacuolated. Observed 48 hours after irradiation (*Right.*)

which occurred during seven hours' incubation did not grow further, and the new cells degenerated during 19 hours' exposure to 693.93 mg. radium.

Active growing cultures of embryo chick heart as well as of heart from young rats entirely degenerated while exposed to radiation of 693.93 mg. radium. (The photomicrographs shown in Figures 10, 11, and 12 demonstrate the results of the experiment with radium.)

On the basis of the results obtained with our set-up of 693.93 mg. radium element, we can consider the amount of radiation given during 13 hours, *i.e.*, 9,022 mg.-hr., as the sublethal dose, and the amount of radiation given during 19 hours, *i.e.*, 13,186 mg.-hr., as the lethal dose for explants and active growing fibroblasts of embryo chick heart and of heart from one- to two-day-old rats.

It should be emphasized here how much of a rôle the intensity factor of radiation plays on the effect of living matter. As previously mentioned, explants of embryo chick heart and of heart from very young rats were able to proliferate for a certain period of time while exposed to 390 mg. radium at a distance of 1.0 cm., but no proliferation at all took place during exposure to 693.93 mg. radium element at the same distance at any time.

It was not the aim of this experiment to determine the equivalent roentgen of x-rays for gamma rays. However, the results obtained from our experiments demonstrate the important fact that our equivalent factor of x-rays for gamma rays for chick and mammalian fibroblasts is similar to those factors found by other investigators for other living subjects.

As previously mentioned, the lethal dose of x-rays for chick and mammalian fibroblasts of embryonic origin was reached with 30,000 r, while the lethal dose with gamma rays was obtained with 19 hours of irradiation of 693.93 mg. radium element. This amount of radium element corresponds to 270 mg. at a point source. By multiplying 270 by 19, the lethal dose can be expressed as 5,130 mg.-hours. This corresponds to the lethal dose obtained with 30,000 r. The equivalent factor of x-rays for gamma rays (r/mg.-hr.) obtained from our experiments is therefore $\frac{30,000}{5,130} = 5.85$. This factor lies directly within the range of findings obtained by other investigators, as shown in Table I:

TABLE I

| | | | |
|---|---|---|---|
| Braun (1930) | *Ascaris* eggs | killing | 5.3 |
| Holthusen and Hamann (1932) | skin | erythema | 5.3 |
| Neeff (1934) | skin | erythema | 5.7–6.3 |
| Exner and Packard (1935) | *Drosophila* eggs | killing | 5.0 |
| Henshaw and Francis (1936) | *Drosophila* eggs | killing | 5.4 |

Our equivalent factor for chick and mammalian fibroblasts is 5.8.

Attention should be called to the fact that a gap has to be filled in our experiments, *i.e.*, to determine the effective doses of gamma radiation between 13 and 19 hours as well as of x-rays between 25,000 r and 30,000 r. It is possible that the lethal dose for the tissues used in our experiments could be reached with 16, 17, or 18 hours' gamma radiation with our radium set-up as well as with 26,000, 27,000, or 29,000 r. This, however, will not change the factor materially. Since the radium capsule of 303.93 mg. was available for only a limited period of time, this experiment could not be completed before this limited time expired.[2] We hope to be able to continue this experiment in greater detail in the near future.

## EXPERIMENT WITH UNFILTERED RADON BULBS

Cultures of embryo chick heart, heart and kidneys from one- to two-day-old rats were used for this experiment, the major

[2] We wish to express our thanks to the Radium Chemical Company for their loan of the radium capsule.

part of the work being carried out with explants of the above-mentioned tissues. In some instances cultures with 24- or 48-hour active growth of new cells were used. The cultures were irradiated in the same lead chamber (Fig. *A*) as used for the previous experiment, with radium at 37.5° C. and 0.5 cm. distance from the unfiltered radon bulb. As a rule we have started with small amounts of radon, increasing the dose until a definite effect upon tissue growth *in vitro* was reached.

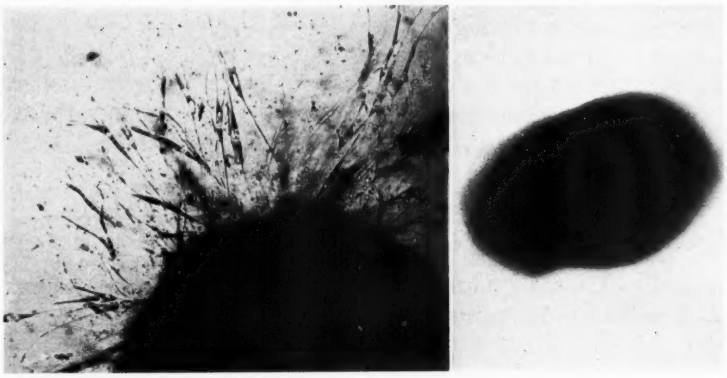

Fig. 13. An explant of embryo chick heart exposed to an unfiltered radon bulb containing 71.13 millicuries for 23 hours and 30 minutes at 0.5 cm. distance. A new growth occurred under radiation, but the newgrowth was smaller and thinner than that of the control cultures. The cells did not have a healthy appearance; many were vacuolated. Culture received 1,541 millicurie-hours. (*Left.*)

Fig. 14. An explant of embryo chick heart exposed to radiation of 102.1 millicuries unfiltered radon bulb at 0.5 cm. distance for 23 hours and 30 minutes. Note absence of growth and outwandering cells. Culture received 2,200 mc.-hours. (*Right.*)

The experiment was started with an unfiltered radon bulb containing 27.6 millicuries. Explants of 8-day-old embryo chick heart were irradiated for one hour and 15 minutes, receiving 34.5 millicurie-hours, and others for three hours, receiving 82.8 millicurie-hours. Growth occurred in the irradiated explants following 24 hours' incubation, showing that there was no apparent difference in comparison with the newgrowth of the control cultures. A culture with 24-hour growth *in vitro* was put under radiation of an unfiltered radon bulb containing 26.77 millicuries for 24 hours. This culture received 585.6 millicurie-hours of gamma and beta radiation. The growth of the culture increased in size during radiation. The new cells, however, especially in the periphery of the margin of the newgrowth, looked unhealthy, and many fat droplets were present.

For the next experiment an unfiltered radon bulb consisting of 59.7 millicuries was used. An explant of embryo chick heart irradiated for three hours and 20 minutes, receiving 191 millicurie-hours, showed a good growth following 24 hours' incubation. Another explant of embryo chick heart produced new growing cells during 16 hours' exposure to an unfiltered radon bulb of 56.85 millicuries, receiving 858 millicurie-hours. The newgrowth, however, was much thinner and smaller in this culture than that of the control cultures and many cells were vacuolated.

In our further experiments—which were rather extensive—we have found that explants of embryo chick heart exposed to an unfiltered radon bulb containing 102.1 millicuries at 0.5 cm. distance did not show any newgrowth or outwandering cells during 23 hours and 30 minutes' radiation, receiving 2,200.0 millicurie-hours. The culture did not recover, *i.e.*, no growth occurred in this irradiated culture following 48 hours' incubation at 37.5° C. While another explant of embryo chick heart exposed to an unfiltered bulb containing 71.1

millicuries radon at 0.5 cm. distance for 23 hours and 30 minutes, receiving 1,541 millicurie-hours, showed a small, thin growth of new cells, and some outwandering cells were scattered in the field. Since these two radon bulbs did not differ widely in the amounts of radon and the explants were exposed for the same time, it seems to us that the lethal dose for chick embryonic fibroblast lies between 1,532.0 and 2,200.0 millicurie-hours. The dose of 1,532.0 millicurie-hours can be regarded as a sublethal one. Similar observations were made when explants of the heart from young rats were exposed to the same amount of radiation. Figures 13 and 14 demonstrate this experiment.

Summarizing, the results obtained in our experiment for the sublethal and lethal doses for chick and mammalian fibroblasts are described in Table II.

The results obtained in these experiments should be considered only for these types of tissues, as mentioned in the text under the circumstances described above.

TABLE II

| Sources of Radiation | Sublethal Dose | Lethal Dose |
|---|---|---|
| X-rays | 20,000 r | 25,000–30,000 r |
| Gamma Rays | 9,022 mg.-hr. | 13,186 mg.-hr. |
| Radon (unfiltered) | 1,532 mc.-hr. | 2,200 mc.-hr. |

### THE EFFECT OF UNFILTERED RADON ON CELL RESPIRATION *in vitro*

In regard to the effect of irradiation on cell respiration *in vitro*, a brief report will be made here.

Kidneys of three- to four-month-old mice irradiated with doses ranging from 3,000 to 6,000 millicurie-hours unfiltered radon showed a decrease in oxygen uptake between 30 and 50 per cent. A more detailed report on this subject will be given in a separate article.

# THE EFFECT OF RADIATION ON CELL RESPIRATION

## I. RESPIRATION AND ANÆROBIC GLYCOLYSIS OF MOUSE KIDNEY *IN VITRO* FOLLOWING RADIATION[1]

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*New York City*

From the Division of Cancer, Department of Hospitals, City of New York, Ira I. Kaplan, M.D., Director; in association with the Department of Experimental Surgery, New York University Medical College, Frank CoTui, M.D., Director, and the Third Surgical Division, Arthur M. Wright, M.D., Director

THE purpose of this experiment was to correlate the effect of various types of radiation on the growth and respiration of mammalian tissues *in vitro*. The results of the effect of x-rays, radium, and radon upon growth *in vitro* are recorded in a separate paper. We were able to determine the lethal dose and sublethal dose of these three types of radiation for tissues of various origin grown *in vitro*. As in the experiments on proliferation, we have also attempted to determine the effective dose of radiation for respiration.

### MATERIAL AND EXPERIMENTAL PROCEDURE

In a previous communication (1) we reported the values of $O_2$ uptake and the respiratory quotients of normal mouse kidneys which showed the most uniform respiration. This type of tissue was, therefore, selected for the experiment with radiation. The kidneys removed under aseptic precautions from three- to four-month-old mice, immediately after pitting, were placed in hollow ground Maximov's slides, a small strip of moist filter paper was placed beside the kidneys in order to avoid evaporation, then covered with a sheet of mica sealed with paraffin wax and exposed to radiation. The reason for using Maximov's slides was because the same equipment was used here as for radiation of the tissue cultures. Since a marked decrease in respiration of normal kidneys was observed when they were kept at room or body temperature for several hours and a very slight decrease in respiration when they were kept at 4° C., the radiation, therefore, was administered at 4° C. While one kidney was exposed to radiation at about 4° C., the other was kept in the refrigerator as a control. After a certain dose of radiation was administered, the kidneys were immediately prepared for respiration *in vitro*. A Ringer-phosphate solution containing 0.2 per cent glucose and at *p*H 7.4 was used as a nutritive medium. The respiratory exchanges of the tissue were determined by the use of the Barcroft-Warburg manometric apparatus. An improvement in this apparatus which we have found increases the precision of the measurements and saves more than one hour will be briefly described here. The Barcroft-Warburg apparatus consists of 14 vessel manometers which are normally used for each experiment. For the determination of respiratory exchanges of tissues, each vessel manometer is saturated for several minutes with a gas (with $O_2$ for ærobic and $N_2$ for anærobic glycolysis). The improvement consists of cross-shaped glass tubes which are connected to each other and to the manometers with rubber tubing. The flow of gas to each vessel manometer is regulated with a screw clamp. When these clamps are once regulated so that the pressure in all vessel manometers is uniform, they need no further attention in the subsequent experiments. Before each experiment the glass tubes are attached to the vessel manometers, the whole system is connected with a gas-tank, and the saturation with gas takes only a few minutes. Figure 1 shows the whole system

[1] See Figures *A* and *B* in Dr. Goldfeder's paper on page 76 of this issue.

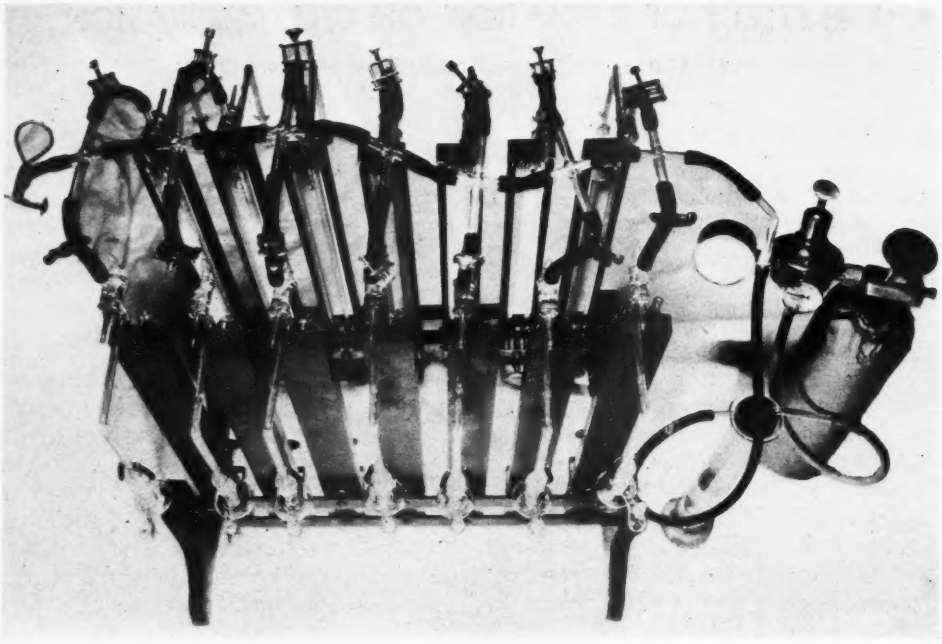

Fig. 1.

and Figure 2 shows the cross-shaped glass tube. Since this technical improvement not only increases the accuracy of the results because the tissue is kept about an hour less at the room temperature before

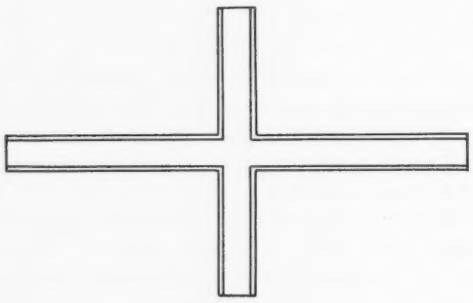

Fig. 2.

the real experiment starts, but also saves so much time for the research worker that we think it is worth while to mention it here and to recommend it to other workers in this field.

Before each experiment the water bath is regulated to 37.5° C., the whole apparatus is set up, the Ringer-phosphate solution placed in the vessels shortly before the radiation of the tissue is completed, the tissues (both control and radiated) are minced or sliced with a very sharp razor, and samples, weighed out on a torsion balance, are placed in the vessels containing the nutritive medium, which are subsequently attached to the manometers. The whole system is then saturated with gas so that no more than from 20 to 30 minutes elapse from the time that the radiation was discontinued until the respiration of the tissues, both irradiated and control, starts in the vessel manometers at body temperature.

### EXPERIMENT WITH X-RAYS

A half wave tube generator and a thin-walled Coolidge tube were used as the source of x-rays. The kidneys were irradiated at a focal distance of 40 cm., using 200 kv., 6 ma., with 1 mm. alumi-

num filter (effective wave length 0.32 Å.). Under these conditions, the average intensity was 80.75 r/min. measured in air. For each experiment a pair of kidneys was used. Each kidney, removed from the mouse immediately after pitting, was sealed in a separate Maximov slide as previously described. One slide containing the kidney was immediately placed in a wooden frame above ice cold water and exposed to radiation; the other was placed in a refrigerator. In this way the temperature of both kidneys was kept between 4° and 5° C. Since the kidneys were kept above water during radiation, 35 per cent of back-scattering was taken into consideration in calculating the total dose. It should be mentioned that the doses of x-rays were administered at once, not fractionated. The first experiment was carried out with 1,800 r. Since no appreciable difference could be observed in the $O_2$ uptake and the respiratory quotients of the irradiated kidney in comparison with that of the control, the further experiments were carried out with increasing doses of x-rays up to 30,000 r. No marked effect was noted on the respiratory exchanges of the irradiated kidneys within the range of the administered dose, from 1,800 to 30,000 r, inclusive. As an example, the results of three experiments are recorded in Table I. No marked difference can be observed between the values of $O_2$ uptake and respiratory quotients of the irradiated and control kidneys. In order to reach larger doses of radiation a longer time of exposure or different equipment for the source of x-rays would be necessary. Due to the lack of technical facilities, it was impossible to continue these experiments at present. However, the following interpretation of the results obtained thus far can be made.

Some investigators observed an increase in the $O_2$ uptake of tissues which had been irradiated with small doses of x-rays; others, however, noted a decrease. For instance, Heeren and Pansdorf (2) observed an increase of 25 per cent in $O_2$ uptake of the irradiated mouse kidney investigated immediately after irradiation. Dognon (3) claims from his experiments with irradiated kidneys of guinea pigs that a decrease in $O_2$ uptake occurs following irradiation with 1,000 r.

In accordance with our observations, no such conclusions can be drawn. Neither a decrease nor an increase was observed in the $O_2$ uptake and respiratory quotient of the mouse kidney following irradiation with from 1,800 r to 30,000 r, inclusive, in our experiments. The results of the effect of x-rays on growth of various tissues were reported in a separate article. (See foregoing paper by A. G.) We were able to demonstrate that fragments of kidneys from one- to two-day-old mice or rats irradiated with 30,000 r showed only a slight growth of epithelial cells during two to three days' incubation at 37.5° C. following irradiation, while control cultures showed an abundant growth of new cells. Since kidneys of three- to four-

TABLE I.—OXYGEN CONSUMPTION AND RESPIRATORY QUOTIENTS OF MOUSE KIDNEY IRRADIATED AT 4° C. WITH X-RAYS *IN VITRO* IN 0.2 PER CENT DEXTROSE RINGER-PHOSPHATE SOLUTION BUFFERED TO *p*H 7.4 AT 37.5° C.

(For each experiment, 12 to 14 vessels were used and the average results are recorded)

| No. of Experiment | Dose in r | Respiration | | | R.Q. | Respiration of Control Kidneys | | | R.Q. |
|---|---|---|---|---|---|---|---|---|---|
| | | $Q_{O_2}$ in first hr. | $Q_{O_2}$ in second hr. | Total $Q_{O_2}$ in two hr. | | $Q_{O_2}$ in first hr. | $Q_{O_2}$ in second hr. | Total $Q_{O_2}$ in two hr. | |
| 1 | 1,800 | 3.41 | 3.09 | 6.50 | 0.85 | 3.65 | 3.50 | 7.15 | 0.88 |
| 2 | 6,000 | 3.5 | 3.6 | 7.1 | 0.84 | 3.19 | 3.12 | 6.31 | 0.80 |
| 3 | 30,000 | 3.20 | 2.94 | 6.14 | 0.81 | 2.83 | 3.05 | 5.88 | 0.91 |

month-old mice irradiated with 30,000 r showed a normal respiration, while kidneys of one- to two-day-old mice irradiated with 30,000 r showed only a slight growth, the question, therefore, arises: Is a higher dose of irradiation necessary in order to affect respiration than is necessary for checking proliferation or is adult tissue more resistant to a given dose of x-rays than that of embryonic origin? We hope to answer this question by further experiments.

### EXPERIMENT WITH RADIUM

The same procedure and technic as used for the experiments with x-rays were applied here, *i.e.*, the kidneys removed immediately after pitting from normal mice were placed in separate Maximov slides, covered with mica sheets and sealed with paraffin wax. One slide, containing the kidneys, was exposed to radiation; the other kept for control. A lead chamber was used here as has been used for the experiment with tissue cultures (Fig. *A*). Figure *B* illustrates the geometrical arrangement of the radium elements. The tissues were irradiated at a distance of 1 cm. The first two experiments were carried out with 300 mg. radium. The kidneys were irradiated in the incubator at 37.5° C. In the first experiment the kidney was exposed for one hour and 25 minutes, receiving 375 mg.-hr.; in the other experiment for two hours, receiving 600 mg.-hr. The control kidneys were kept in a separate incubator at 37.5° C., while the others were irradiated. The results obtained in the experiment with radium are recorded in Table II. As can be seen from Experiments No. 1 and No. 2, no marked difference in oxygen uptake of the irradiated and control kidneys occurred, but a low respiration of both kidneys was noted, due to the temperature.

On the basis of these observations that kidneys kept for longer periods of time at 37.5° C. show a decrease in $O_2$ uptake, while those kept in the icebox for 24 hours show only a slight decrease in $O_2$ uptake, the radiation of the kidney tissue in our further experiments was, therefore, administered in an icebox at 4° C. Kidneys irradiated with 300 mg. radium, for four hours at 4° C., receiving 1,200 mg.-hr., showed no marked difference in oxygen uptake from the control kidneys. (See Experiment No. 3, Table II.)

Since no marked change in $O_2$ uptake was observed by using the amounts of irradiation mentioned above, the amount of radium element was increased in order to increase the dose and to avoid a longer time of exposure. Experiments No. 4 and No. 5 were carried out with 390 mg. radium, to which, in Experiment No. 4, the kidney was exposed for four hours, receiving 1,560

TABLE II.—OXYGEN CONSUMPTION AND RESPIRATORY QUOTIENTS OF MOUSE KIDNEY RADIATED WITH RADIUM AT 4° C. *IN VITRO* IN 0.2 PER CENT DEXTROSE RINGER-PHOSPHATE SOLUTION BUFFERED TO *p*H 7.4 AT 37.5° C.

(For each experiment, 12 to 14 vessels were used and the average results are recorded)

| No. of Experiment | Dose in Mg.-hr. | Respiration | | | R.Q. | Respiration of Normal Control Kidneys | | | R.Q. | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $Q_{O_2}$ in first hr. | $Q_{O_2}$ in second hr. | Total $Q_{O_2}$ in two hr. | | $Q_{O_2}$ in first hr. | $Q_{O_2}$ in second hr. | Total $Q_{O_2}$ in two hr. | | |
| 1 | 375 | 1.01 | 0.77 | 1.8 | | 1.09 | 1.1 | 2.1 | | The calculations were made on wet weight of the kidney tissue. In Experiments No. 1 and No. 2 the kidneys were irradiated at 37.5° C. |
| 2 | 600 | 0.18 | 0.66 | 1.44 | | 1.1 | 0.8 | 1.1 | | |
| 3 | 1,200 | 3.71 | 2.93 | 6.76 | | 3.76 | 3.8 | 7.92 | | |
| 4 | 1,560 | 2.3 | 2.4 | 4.6 | 0.94 | 3.8 | 3.8 | 7.6 | 0.84 | |
| 5 | 1,657 | 2.3 | 2.5 | 4.51 | 0.86 | 2.6 | 2.5 | 5.1 | 0.89 | |
| 6 | 3,470 | 3.3 | 3.4 | 6.3 | 0.89 | 3.4 | 2.8 | 6.2 | 0.85 | |
| 7 | 4,164 | 2.5 | 2.3 | 4.8 | 0.86 | 2.7 | 2.6 | 5.3 | 0.86 | |

mg.-hr., and in Experiment No. 5 the kidney was exposed for four hours and 15 minutes, receiving 1,657 mg.-hr.

No marked change in oxygen uptake and respiratory quotient occurred in the irradiated kidney in comparison with that of the control kidney. Experiments No. 6 and No. 7 were carried out with 693.93 mg. radium.

In Experiment No. 6 the kidney was irradiated for five hours at 4° C., receiving 3,470 mg.-hr., and in Experiment No. 7 for six hours, receiving 4,164 mg.-hr. No marked difference either in oxygen uptake or in the respiratory quotients could be observed in either experiment when compared with that of the control kidneys. It should be mentioned here that the tissue received only gamma radiation from our radium set-up. As computed by C. B. Braestrup, our physicist, the radiation from the 693.93 mg. radium element is equivalent, at the center of the culture, to that from a point source of approximately 270 mg. at 1.0 cm. distance and 0.5 mm. platinum filter.

Due to the limited time of the loan of radium from the Radium Chemical Company, in New York City, the experiment with radium had to be discontinued for the present.

Comparing the results obtained from the effect of gamma irradiation upon proliferation, it can be seen that the amount of irradiation which apparently did not affect the proliferation also did not affect the respiration. However, there was a difference in the temperature at which the tissues were kept while being exposed to irradiation. The proliferating tissues were irradiated at 37.5° C., while the tissues used for respiration were exposed to irradiation at 4° C.

Halberstädter and Doljanski (4), in a recently published article, reported results which they observed of the effect of irradiation with radium on explants of chick embryos. They reached the conclusion that tissue fragments exposed to irradiation *in vitro* at a low temperature accumulate more radium than while in a stage of proliferation at 37.5° C. They were able to prevent emigration and proliferation of cells from the irradiated fragments *in vitro* at a low temperature with much smaller doses than are required to obtain the same effect while these fragments are exposed at body temperature.

Although the amount of radiation administered by us to the mouse kidney at a low temperature was much higher than that used by the above mentioned authors, yet no effect on respiration could be observed. However, in discussing this phenomenon two possibilities have to be taken into consideration: (1) Halberstädter and Doljanski have used chick embryonic tissue for their experiments, while we have used mammalian adult tissue; (2) with their set-up of radium element the tissues received a certain amount of beta rays which are more effective than gamma rays, while with our set-up only gamma rays can be considered. Another possibility is that a larger dose of irradiation is necessary to affect the metabolism of cells than is required to check their proliferation.

From further experiments which we have in progress, we hope to be able to throw more light on this problem.

### EXPERIMENT WITH UNFILTERED RADON BULBS

As previously mentioned, various experiments were carried out with x-rays and radium on the effect of respiration of living matter. However, no data could be found in the literature concerning the effect of radon (gamma plus beta rays) on cell respiration and glycolysis *in vitro*. Since no definite results could be reached on the effect of radiation on cell respiration *in vitro* by means of x-rays and radium with our set-up, a series of experiments were undertaken with the use of unfiltered radon bulbs. The same type of tissue, *i.e.*, the kidneys of three- to four-month-old mice, was exposed in Maximov slides immediately after removal from the animal body, to various amounts of beta plus gamma radiation. The kidneys were irradiated in the same lead chamber (Fig. *A*) as used

TABLE III.—OXYGEN CONSUMPTION AND RESPIRATORY QUOTIENTS OF MOUSE KIDNEY IRRADIATED AT 4° C. WITH UNFILTERED RADON *IN VITRO* IN 0.2 PER CENT DEXTROSE RINGER-PHOSPHATE SOLUTION BUFFERED TO *p*H 7.4 AT 37.5° C.

(For each experiment, 12 to 14 vessels were used and the average results are recorded)

| No. of Experiment | Dose in Mc.-hr. | Respiration | | | R.Q. | Respiration of Normal Control Kidneys | | | R. Q. | Decrease in $O_2$ of Irradiated Kidneys in Percentage | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $Q_{O_2}$ in first hr. | $Q_{O_2}$ in second hr. | Total $Q_{O_2}$ in two hr. | | $Q_{O_2}$ in first hr. | $Q_{O_2}$ in second hr. | Total $Q_{O_2}$ in two hr. | | | |
| 1 | 1,180 | 1.84 | 1.38 | 3.22 | 0.9 | 2.7 | 2.5 | 5.2 | 0.85 | 36 | The decrease in respiration of the irradiated kidneys is more marked in the second hour of respiration. |
| 2 | 3,936 | 1.32 | 0.66 | 1.98 | 0.87 | 2.3 | 2.0 | 4.4 | 0.84 | 50 | |
| 3 | 3,334 | 1.72 | 1.0 | 2.72 | 0.84 | 2.1 | 2.1 | 4.2 | 0.92 | 45 | |
| 4 | 6,710 | 1.47 | 0.74 | 2.21 | 0.82 | 3.2 | 2.8 | 6.1 | 0.83 | 64 | |
| 5 | 6,546 | 1.54 | 0.76 | 2.16 | 0.81 | 2.5 | 2.3 | 4.8 | 0.89 | 56 | |
| 6 | 5,118 | 1.60 | 0.84 | 2.44 | 0.78 | 1.9 | 2.1 | 4.0 | 0.89 | 40 | |
| 7 | 3,822 | 2.48 | 1.66 | 4.14 | 0.83 | 3.1 | 2.6 | 5.7 | 0.84 | 30 | |

for the experiment with radium, at a temperature of 4° C. at 0.5 cm. distance.

As usual, while one kidney of the mouse was irradiated, the other was kept in a moist and sealed Maximov slide in a separate icebox. In order to reach an effective dose, high doses of irradiation were necessary. For this reason, in most instances, the kidneys were left over night in the iceboxes. As previously mentioned, only a slight decrease in respiration occurred in normal kidneys when kept over night in the icebox, whereas when kept at room temperature or at 37.5° C. a much greater fall in metabolism occurred.

In Table III are recorded the values of $O_2$ uptake and respiratory quotients of both irradiated and normal kidneys from each mouse. As can be seen from the data, a marked decrease in the oxygen uptake occurred in the irradiated kidneys, but no marked change in the respiratory quotients was observed when compared with the corresponding values of the control kidneys. A rapid fall in respiration particularly occurred during the second hour of respiration *in vitro*.

This phenomenon was also observed by Dognon, *l.c.*, in his experiments with a dose of 20,000,000 r. The decrease in $O_2$ uptake of the irradiated kidneys corresponds to the increase of the dose administered with one exception. In Experiment No. 3 the kidney received 3,334 mc.-hours which produced a reduction in $O_2$ uptake of 45 per cent, while in Experiment No. 7, when the kidney received 3,822 mc.-hours the decrease in $O_2$ uptake was only 30 per cent. This may have been an artefact.

Several experiments were carried out to observe the effect of unfiltered radon on anærobic glycolysis. The same experimental procedure was used here as for the previous experiments with the exception that the vessel manometers containing the tissue were saturated with a gas mixture of 95 per cent $N_2$ and 5 per cent $CO_2$ and a bicarbonate Ringer solution, as originally advised by Warburg for anærobic glycolysis, was also used here. Since the $CO_2$ evolved as indicated

by the pressure in the manometers does not correspond specifically to the amount of lactic acid formed by the tissue, particularly of kidneys, because of the presence of a certain amount of ammonia, the amount of lactic acid formed by the tissues, irradiated and control, during two hours was determined in the medium by the chemical method of Friedemann-Graeser (5). We have followed this method precisely as recommended by the authors; no description, therefore, will be given here.

In Table IV are recorded the results obtained from the effect of unfiltered radon on anærobic glycolysis. As can be seen from these results, the decrease in anærobic glycolysis increases with the dose of radon administered to the tissue but not in as narrow a range as was observed in the experiments on respiration. Comparing the results recorded in Table III and Table IV, the following facts are apparent: (1) The percentage of decrease in oxygen uptake corresponds directly with the increase in the amount of radiation administered within a narrow range, while in the anærobic glycolysis this is not the case. For example, Experiment No. 3 (Table IV) received 6,736 mc.-hr. and showed a decrease of 83 per cent in the amount of lactic acid as compared with that of the normal kidneys, while Experiment No. 5 which received 7,727 mc.-hr. showed a decrease of only 84 per cent, although the dose exceeded the former by about 1,000 mc.-hours. On the other hand, we see an agreement between the results of the Experiments No. 3 and No. 4 in which doses of radon are approximately the same. (2) Approximately the same dose of radon produced a greater decrease in anærobic glycolysis than in respiration, as can be seen from Experiment No. 4 in Table III and from Experiment No. 3 in Table IV.

## SUMMARY AND CONCLUSION

A study was undertaken to investigate the effect of various types of radiation on growth and respiration *in vitro* of mammalian tissues. The effect upon growth of various tissues was reported in a separate article. The results obtained thus far on the effect of respiration and anærobic glycolysis are being reported here. As an index, the normal mouse kidneys were used for this experiment. The types of radiation employed were high voltage x-rays, gamma rays from radium, and radon (gamma plus beta rays). For the determination of the oxygen uptake and respiratory quotients the Warburg manometric apparatus was used. Friedemann-Graeser's method was used for the determination of lactic acid. The kidneys were irradiated *in vitro* at 4° C. No appreciable effect on respiration and on the respiratory quotients could be observed with the arrangement of radium and x-rays as used by us thus far. For example, with 4,140 mg.-hr. of gamma radiation and 30,000 r units of x-rays, no effect on kidney

TABLE IV.—ANÆROBIC GLYCOLYSIS OF MOUSE KIDNEY IRRADIATED AT 4° C. WITH UNFILTERED RADON *IN VITRO* IN 0.2 PER CENT DEXTROSE BICARBONATE RINGER SOLUTION BUFFERED TO *p*H 7.4 AT 37.5° C.

| Irradiated Kidneys | | | Control Kidney Mg. Lactic Acid per Mg. Tissue 2 Hr. | Decrease in Lactic Acid of Irradiated Kidneys in Percentage |
|---|---|---|---|---|
| No. of Experiment | Dose in Mc.-hr. | Mg. Lactic Acid per 1 Mg. Tissue 2 Hr. | | |
| 1 | 1,949 | 0.00387 | 0.00748 | 48 |
| 2 | 3,050 | 0.00220 | 0.0065 | 65 |
| 3 | 6,736 | 0.00090 | 0.0053 | 83 |
| 4 | 6,720 | 0.00266 | 0.01682 | 84 |
| 5 | 7,727 | 0.00067 | 0.00431 | 84 |

respiration of adult mice was obtained. A definite effect on respiration and anærobic glycolysis was observed when the kidneys were irradiated with unfiltered radon. With doses ranging from 4,000 to 6,500 mc.-hr. of gamma plus beta radiation a decrease in $O_2$ uptake between 40 and 60 per cent was observed, without any effect, however, on the respiratory quotients, while doses ranging from about 2,000 to 7,700 mc.-hr. produced a decrease in anærobic glycolysis ranging between 50 and 84 per cent.

As can be concluded from this experiment, a high dose of irradiation is necessary to produce an effect on respiration of living matter—in this case of adult mouse kidneys—and a still higher dose to affect the respiratory quotient. In other words, the respiration of the living cells can be affected without producing a marked change in the respiratory quotient. This observation contradicts the hypothesis of H. Rudisill and J. H. Hoch[2] that the biological effect of irradiation on cells may result from the effects of the substances, so-called co-catalysts present in the cells.

Another point which should be emphasized here is as follows: Many investigators believe in a delayed effect of radiation on living processes, *i.e.*, that the effect of various rays is not a direct but rather a delayed one, produced by secondary changes in the living matter. The results obtained by us in the experiment with radon indicate that the effective dose of radiation on living processes depends on the action of the specific rays and the dose administered. From our experiments it can be seen how much more effective the beta rays are than the x-rays or gamma rays alone and how through the beta rays a direct effect on cell respiration and anærobic glycolysis can be obtained. With a dose of 30,000 r and with a dose of 4,164 mg.-hr. of gamma rays alone, no effect on respiration and respiratory quotient was observed, while a corresponding dose of 3,936 mc.-hr. of beta plus gamma rays produced a decrease in respiration of 50 per cent.

Comparing the effect of unfiltered radon on proliferation and respiration the following observations were made. A dose of 2,200 mc.-hr. of unfiltered radon administered to an explant of a kidney from one-day-old rats or mice entirely inhibited the proliferation of this explant, while a dose of 6,710 mc.-hr. administered to a kidney from about a four-month-old mouse produced a reduction of only 64 per cent in $O_2$ uptake. The question arises whether a higher dose is necessary to inhibit the proliferation of the cells than their respiration, or is adult tissue more resistant to a given dose of radiation? Through further experimentation, using tissues of embryonic and other origin which are in progress at present, we hope to be able to answer this question and to throw more light on the effect of various rays on living processes.

Our grateful thanks are herewith expressed to Ira I. Kaplan, M.D., and to Frank CoTui, M.D., for their kind cooperation and interest in making this work possible. We also are indebted to Carl B. Braestrup, physicist for the Division of Cancer, Department of Hospitals, City of New York, and his associates for their helpful advice and assistance, and we wish to thank the Works Progress Administration for the loan of the Warburg manometric apparatus used for these experiments and Warner, Schering, and Glatz, Inc., for financial aid.

[2] A paper presented at the Fifth International Congress of Radiology, September, 1937.

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# GENERATORS FOR GAMMA RAYS AND NEUTRONS AND RADIOTHERAPEUTIC POSSIBILITIES[1]

*By* A. BOUWERS, D.Sc., *Eindhoven, Holland*

From the X-ray Research Laboratories, N. V. Philips' Gloeilampenfabrieken

THE technic of high voltage generators and high voltage discharge tubes for the production of penetrating x-rays has been successfully applied to nuclear physics. In fact, generators for one million volts and more, designed to produce x-rays by accelerating electrons (the usual way), can be used to accelerate positive particles merely by reversing the tension.

Positive particles may be produced by voltages of the order of 50 kv. in tubes not essentially different from the good old gas tubes, the positive ions emerging through a hole in the cathode. These positive ions (canal rays) are protons if the gas in the discharge tube is hydrogen, deutons in the case of heavy hydrogen, and $\alpha$-particles in the case of helium.

The acceleration of the positive particles takes place in a tube which shows, as we shall see in more detail later on, a great analogy with a high voltage x-ray tube.

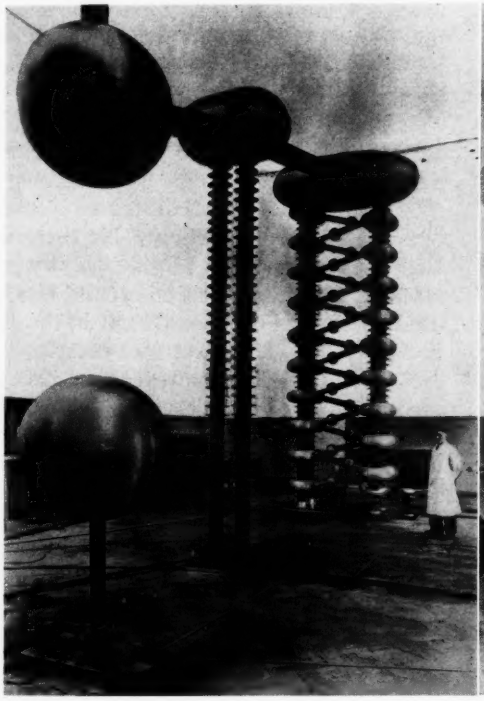

Fig. 1.

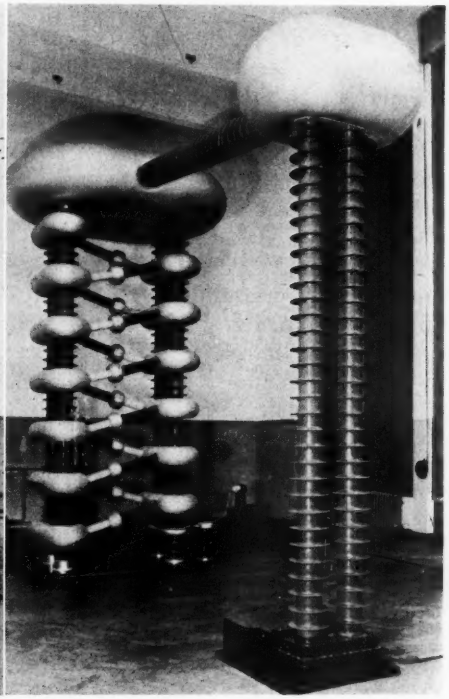

Fig. 2.

At the other hand, the results of nuclear physics have stimulated further development of high voltage technic. Generators for voltages of many millions of volts have been designed. The first interesting nuclear reaction by means of high voltage was performed by Cockcroft and Walton in 1932 (1). The lithium nucleus was split up into two helium nuclei or $\alpha$-particles by means of protons accelerated with

[1] Read before the Fifth International Congress of Radiology, at Chicago, September, 1937.

a voltage of some hundreds of kilovolts. It was shown later that this reaction is possible with voltages as low as 10 kv. (2, 3); but the output increases rapidly with the voltage, as is the case for most nuclear reactions. Moreover, many reactions cannot be expected to take place below certain minimum voltages. So, for instance, may a beryllium nucleus be split up by x-rays or $\gamma$-rays equivalent to one and a half million volts as a minimum value. At voltages of little over one million volts (1 mv.) a very interesting phenomenon appears: a gamma quantum is transformed into a pair of particles, a positron and an electron. The production of x-rays ($\gamma$-rays) of one million volts becomes extremely efficient, the output at one million volts being equivalent to more than 1 kg. of radium at 1 ma. tube current.

A short description of a high voltage generator developed by the author, given at the American Congress of Radiology in 1933, has been published (4). This generator has been further developed up to a voltage of four million volts. A full description has been published recently (5). The article contains also a brief critical survey of the other methods to produce fast particles with and without high voltages.

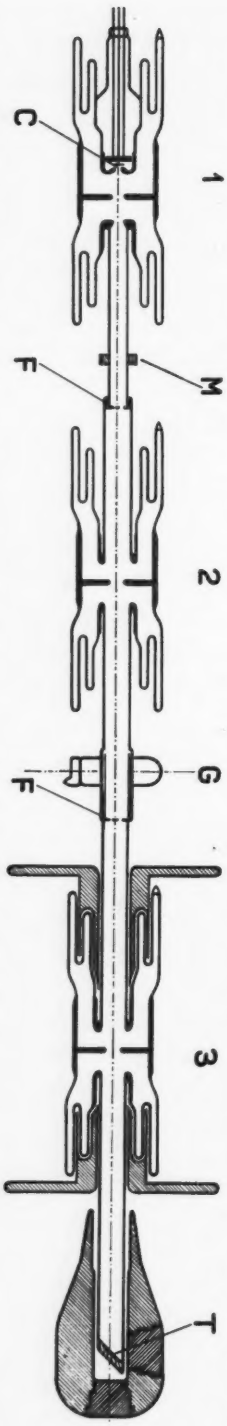

Fig. 3.

Figure 1 shows a generator of two million volts to earth, being the negative half of a four-million-volts set at the Eindhoven laboratories.

Figure 2 shows a one and a quarter million volts generator delivered to, and in use for many months now at, the Cavendish Laboratory, Cambridge. For further details we refer to the paper mentioned above (4) and proceed to describe—(*a*) A million-volt x-ray or $\gamma$-ray tube of the sealed-off type; (*b*) A high voltage neutron tube.

(*a.*) A sealed-off tube for tensions up to 700 kv. was reported upon by Dr. van der Tuuk and myself (6).

Figure 3 shows the construction of the one-million-volt tube comprising three sections. Electrons are produced by the cathode, C, of the first section, and accelerated to a speed of over 330 kv. in the first division (1). The electrons entering the second section with that speed are accelerated once more in that division (2) and also a third time in the third division (3). The anticathode (T) protrudes outside the tube, making cooling and protection much easier than when in the vacuum as usual. X-rays emerge in an axial direction through the tungsten and copper target with almost the same intensity as at right-angles.

The tube is mounted on a small truck (Fig. 4); two columns contain oil-cooled resistances, carrying a constant current of about 1 milliampere. From this resistance used as potentiometer, the different sections of the tube are tapped off, thus receiving equal parts of the high voltage. The re-entrant parts of the sections are of great importance. They are, in fact, "double re-entrant parts," as may be seen in the drawing. Insulating rings with disks (as only shown in tube 3) are essential with them. They made it possible to reduce the length of every section, tested separately at 400 kv. to about 20 inches.

The sections are closed at the ends with thin foils and exhausted separately. The foils, F, are burned by the electron beam after the sections have been soldered together.

Another essential point is the "getter-device." Several "getters," which may be put into action by means of a filament, are built in a separate metal chamber, G, connected to the tube. One of these "getters" is sufficient to absorb the gas that is freed by the processes of soldering and burning the foils. The tube may, after exhaustion, even be opened—if it is for a short time only—soldered together and evacuated with a portable pump at the spot. The "getters" make further heating superfluous and recover and maintain a perfect vacuum afterward. A ring-shaped permanent magnet, M, is used as a focusing device to keep the beam of electrons central and within a limited cross-section.

Protection against radiation is particularly simple with the protruding anticathode. The lead round it has such a thickness that the radiation from the target has to penetrate at least 6 cm. in every direction. Several windows are provided, which can be closed or opened at will and which allow for treatment or measurement in at least four different directions. Cooling of the target is effected by the oil, that at the same time cools the potential resistances mentioned above.

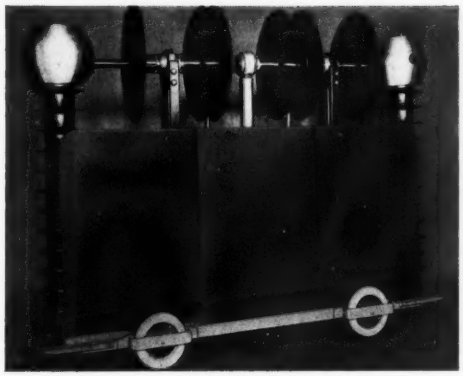

Fig. 4.

The tube is fed by a generator of the cascade type mentioned, giving symmetrical voltage: 500 kv. positive and negative (Fig. 5). The voltage is measured simply by measuring the current through the known resistance parallel to the tube. The anticathode is in this case at a potential of 500 kv. As long as treatment is carried out at a distance of 1 m. or more, patients (three or more at a time) may be placed behind a partition or a wall (serving as protection).

Another arrangement with the anode earthed and the cathode at 1 mv. is also possible with the same tube.

Some measurements have been carried out, which will be reported upon more

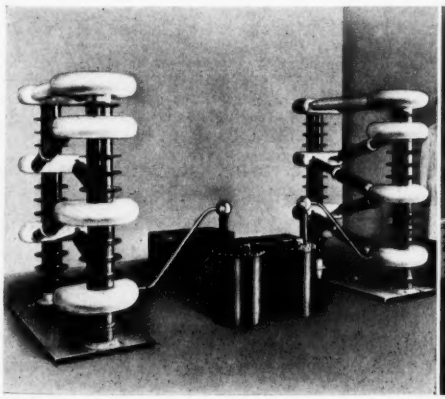

Fig. 5.

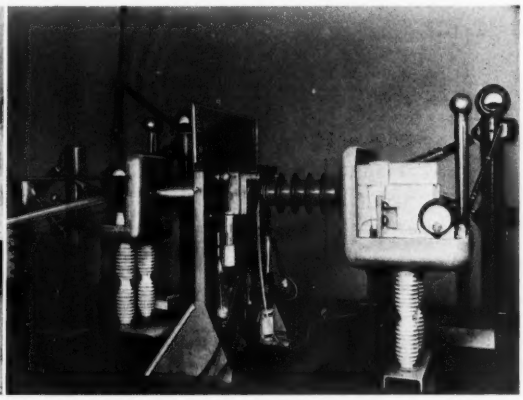

Fig. 6.

fully elsewhere. Two preliminary results may be mentioned here:

1. The half value layer at 870 kv. in copper after a filter of 2 mm. lead, 1 mm. tungsten, and 2.5 mm. copper is found to be approximately 10 mm.

2. The dose at 870 kv. and 1 ma. is equivalent to approximately 1 kg. of radium.

(*b*) The possibilities of neutrons for therapeutic purposes have been mentioned in the literature several times (7, 8, 9, 10). They may be applied either directly or indirectly through the production of artificial radio-active substances. Some biologic researches have been carried out with the neutron source, described in the following. They will be reported upon by Dr. den Hoed at this Congress.

Neutrons were produced by bombarding either beryllium or lithium or heavy hydrogen with deutons. The lithium target was the most effective, as it produced the largest quantity of neutrons—

$$Li_3^7 + H_1^2 \longrightarrow 2He_2^4 + n_0^1.$$

The maximum speed of the neutrons is equivalent to about 14 million "electron volts." These fast neutrons are scattered and slowed down by means of paraffin, as clearly seen in Figure 6, after the Fermi method (11). At each collision with a hydrogen nucleus a certain loss of energy takes place. The result is an increased chance of being captured by nuclei and so, for instance, an increase in output of artificial radio-activity in silver.

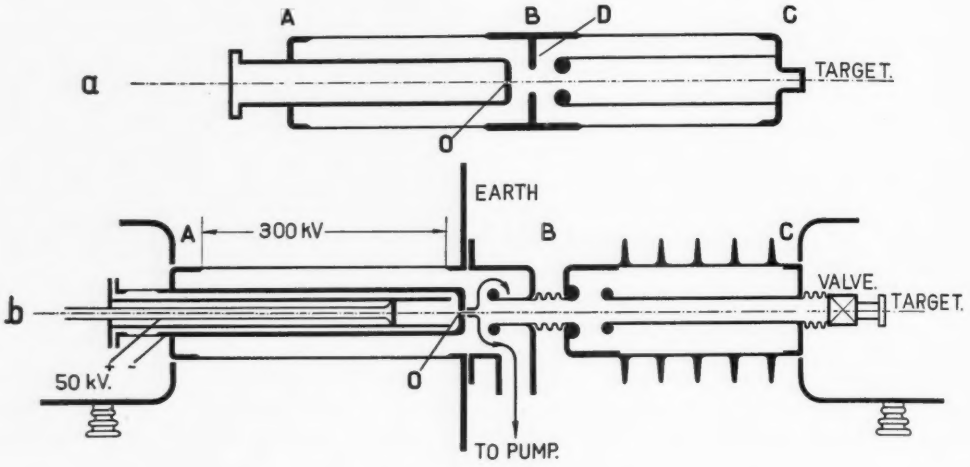


Fig. 7.

In Figure 7, *a* shows the principle of the tube, which is similar to the x-ray tube, just described. The positive electrode, A, contains the ion-source, a 50 kv. canal-ray tube. The ions emerge through a small opening, 0, in the cathode of this tube, which is at the same time the anode of the accelerating section AB. Both the negative and the positive electrodes of the accelerating tube, ABC, are at their ends surrounded by a metal cylinder, B, with a metal partition at earth potential, D, between them. No trouble from secondary electrons is experienced in this way.

The negative electrode consists of a metal tube to conduct the canal-ray to the target. This tube, as opposed to the x-ray tube, described above, must be continuously evacuated in order to remove the hydrogen flowing through the canal from the ion-source into the accelerating tube. For that reason the part B is enlarged and the pump is connected to the tube as indicated in *b* in Figure 7. Also a piece of flexible tubing is placed between the two

parts of the tube in order to permit of the concentration of the canal-ray on the target by moving the second part of the tube.

Another difference with the x-ray tubes lies in the fact that the construction of the ion-source did not allow the use of re-entering parts. At the target-side also the application of the re-entrant principle does not offer any advantages; however, only when more accelerating tubes are used in series does the re-entrant construction become profitable.

It may be mentioned further that, instead of glass for the construction of the second accelerating part, BC, of the tube, we used "Philite," a kind of artificial resin (Fig. 6), which gave quite satisfactory results. For the most delicate part, however (ion-source and first step), chromium-iron-glass joints were always used.

The construction of the ion-source has been described in more detail in a paper by Heyn, Kuntke, and myself (12). While in that paper a neutron output equivalent to 3 grams of radium mixed with beryllium has been stated, with the tube described in two steps of 300 kv. each, we obtained the equivalent of about 300 grams of radium-beryllium.

Preparations are being made for extension to three steps, which is expected to give us more than ten times the output of the present tube, but definite results cannot yet be given.

It is interesting to note that, when using hydrogen and bombarding lithium, emission of $\gamma$-rays takes place at voltages of about 440 kv. (13). These $\gamma$-rays have frequencies equivalent to about 17 mv.

It may be that for very hard $\gamma$-rays this method of production (by nuclear physics) is more practical than the application of still much higher voltages.

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# AN EXPERIMENTAL STUDY OF THE EFFECTS OF ROENTGEN RAYS ON THE GONADS OF THE DEVELOPING CHICK

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From the Department of Anatomy, Loyola University School of Medicine

## INTRODUCTION

OUR knowledge concerning the effects of roentgen rays on the gonads of the developing and adult birds is very limited. Such data as are available have been obtained from studies dealing with x-ray effects on the chick embryo as a whole, and not on a specific study of the gonads. Further, a larger part of the work on birds has been done without standardized x-ray equipment and without adequate correlation of the age of the animal, dosage of x-rays, and results obtained.

We have undertaken to investigate further the problem of the effects of x-rays on the gonads of the bird under standardized conditions. The problem was divided into two parts: (1) The effects of roentgen rays on the developing chick, and (2) the effects on the adult male and female bird. The results of the first experiment are recorded in this paper.

## MATERIALS AND METHODS

The x-ray machine[1] used was mechanically rectified and provided with a Landauer roentgenometer. A Universal Cooldige therapy tube was used. The set-up of the machine for the entire experiment was as follows: The kilowatt meter was set at 96, which delivered 112 kv.p. as measured by the sphere gap; the milliammeter was set at 6 ma.; the focal distance was 10 inches; the filter was equivalent to 4 mm. aluminum; the roentgenometer was kept at 3.2 micro-amperes, which, by calculation, gave 0.6 r per second. The desired r, or dosage, was obtained by varying the time of exposure.

The eggs were x-rayed on a specially designed irradiation box (4), so constructed as to keep them at incubation temperature during irradiation. It included facilities for candling and absorption of scattered rays.

Young chicks were strapped back-down, by means of their wings and legs, on a board in such a manner as to expose the gonadal region and prevent discomfort to the animal.

In all, 121 specimens were used. Of this number, 28 were controls and 93 experimental material. Of the latter, there were 18 eggs irradiated prior to incubation, 26 eggs x-rayed between 5 to 12 days' incubation, and 49 chicks were treated between the time of hatching and 21 days after hatching. Fourteen of the specimens were subjected to superimposed radiation.

All material was fixed in a solution made up of four parts of Kleinenberg's picro-sulphuric acid reagent with one part of 10 per cent formaldehyde, embedded in paraffin and stained with eosin and hematoxylin.

## RESULTS: EGGS IRRADIATED PRIOR TO INCUBATION

This experiment was designed to test the effects of x-rays on the pre-incubational stage of embryonal development as far as the roentgen rays may or may not affect germ cell and gonad formation. The eggs received x-ray dosages varying from 40 to 480 r. All chicks were sacrificed within two weeks after hatching.

*The Testes.*—The development of the testes proved to be only slightly affected by the x-rays in this stage of development. The differentiating seminiferous tubules appeared to be normal in number, size, and stage of development. The interstitial tissue did not deviate perceptibly from that found in the controls. An indication of x-ray injury was found in the vascularization of the testes. The blood vessels,

[1] Type C model, made by the Standard X-ray Company.

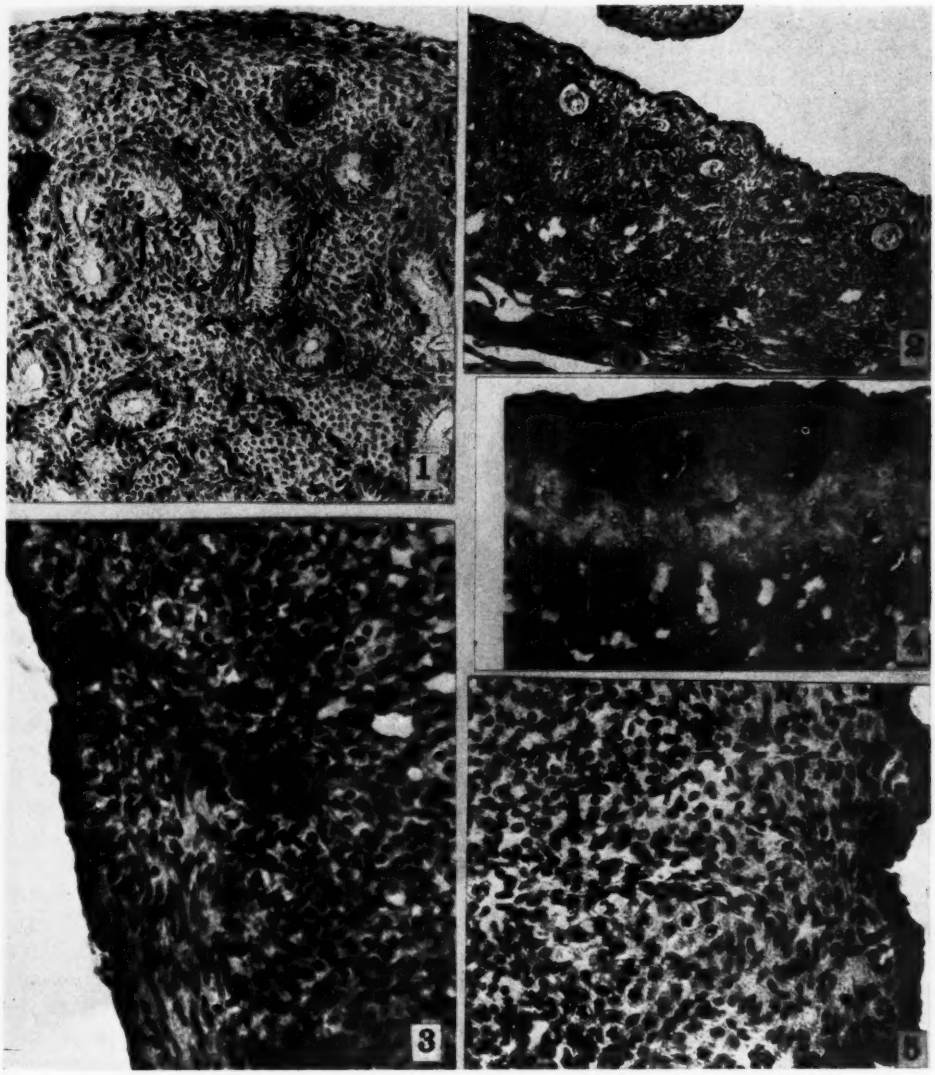


Fig. 1. Section of a testis of a 13-day-old chick showing vascular congestion. Irradiated with 100 r prior to incubation (×275).

Fig. 2. Section of an ovary of a three-day-old chick x-rayed with 100 r before incubation. Note the inactive germinal epithelium, the reduction in germ cells and primary follicles, and the presence of anovular follicles (×187).

Fig. 3. Section of an ovary of a two-day-old chick irradiated with 400 r prior to incubation. Note the inactive germinal epithelium, extreme reduction of germ cells, and excessive tunica albuginea (×510).

Fig. 4. Section of an ovary of a three-day-old chick x-rayed with 120 r prior to incubation, showing necrotic areas in cortex and partly in medulla (×460).

Fig. 5. Section of an ovary of a 18-day-old chick embryo irradiated with 400 r on the fifth day of incubation. Note the scarcity of germ cells and the excessive tunica albuginea (×488).

which were rather inconspicuous in the gonads of the controls, became greatly enlarged and were gorged with blood cells in the treated material (Fig. 1). The extent of the blood congestion varied considerably, however, even in specimens treated to the same dosage of x-rays.

*The Ovaries.*—In all of these experi-

ments the ovaries have invariably shown a greater sensitivity to x-rays than the testes. Except in those treated to very low dosages, 80 r or less, varying degrees of injury could be demonstrated in practically all ovaries irradiated. The less seriously affected ovaries showed reduced mitotic index, inactive germinal epithelium, and reduced number of germ cells in the cortex. The above defects have been observed in the controls but in only a few instances. It must also be stated here that injuries of this type were commonly observed in ovaries treated to dosages in the neighborhood of 100 r; however, similar injuries were met with in ovaries that had received 300 r or more.

In the more severely affected ovaries there was found a marked reduction of primary follicles (Fig. 2). A few follicles were found that lacked the ovum, anovular, the space of which was occupied by follicular cells. In some specimens the ovaries lagged behind in development: in such, there were no follicles of any kind. The germ cells were greatly reduced in number and those that remained were segregated into definite areas or nests. In such ovaries an exaggerated development of the tunica albuginea was noted (Fig. 3).

In one specimen, necrotic areas resembling hyaline degeneration were found at different levels of the ovary (Fig. 4). In the areas so affected the germinal epithelium, the cortex, and to some extent the medulla, were involved. There was a marked reduction of germ cells and follicles in this ovary. Since only one of 18 specimens presented this anomaly, it is likely that the cause was not of x-ray origin.

### EGGS IRRADIATED DURING THE INCUBATION PERIOD

The experiments in this group were arranged to test the effects of radiation on gonad formation. X-rays were applied to eggs between 5 and 12 days of incubation: the dosages varied from 100 to 400 r. About one-half of the specimens were killed on the eighteenth day of incubation, the rest were sacrificed during the first week after hatching.

*The Testes.*—Contrary to expectation, the effects of the x-rays on the testes of this series were minor in nature. The gonads were comparable to those irradiated prior to incubation; the tubules seemed to be normal in size and number; the epithelium, however, lacked the normal appearance and mitosis was seldom noted. The interstitial tissue and the testicular stroma presented no perceptible departure from normalcy except for the presence of vascular congestion. The latter feature was observed more frequently and to a larger extent than in the testes of the former experiment.

*The Ovaries.*—The x-ray injuries in this experiment varied directly with the age of the embryo and the dosage, more consistently than in the ovaries of embryos irradiated prior to incubation. In the ovaries of maximum injury, dosages of 300 to 400 r, age 5 to 7 days' incubation, the oocytes which in normal ovaries of comparable age fill the entire cortex, were found to be very scarce. Instead, the peripheral part of the cortex was occupied by fibroblasts (Fig. 5). Small groups of oocytes, found in the isolated parts of the ovary, were in process of degeneration, as indicated by pyknotic nuclei and colorless cytoplasm. The germinal epithelium of such ovaries was practically one layer of cells in thickness and, of course, showed no signs of germ cell proliferation. In some parts of the cortex condensed masses of cells in the form of cords were noted, such structures always being surrounded by a connective tissue capsule and having a close resemblance to the anovular follicles (Fig. 6).

The ovaries of chick embryos irradiated with dosages ranging from 200 to 300 r, and at ages 5 to 7 days of incubation, presented less severe injuries than those of higher dosages. It was found most commonly that the middle part of the ovary was devoid of oocytes but that such were present in larger numbers at the poles, particularly

the lower pole of the ovary. Such germ cells, however, lacked the appearance of normal cells. An inactive germinal epithelium and cortical fibrosis were common features in this group.

Ovaries of embryos irradiated with dosages less than 200 r at ages more than six days presented minor injuries. At least some of them could not be distinguished from the ovaries of the controls.

IRRADIATION OF CHICKS AFTER HATCHING

In this experiment, it was intended to test irradiation effects on the development of the follicles, seminiferous tubules, and the interstitial cells. These chicks were x-rayed from one to 21 days after hatching, the dosages varying from 80 to 600 r. About half of the chicks were killed within five days after irradiation, the other half was sacrificed within 22 days after hatching.

*The Testes.*—In this experiment, as in the two previous ones, the testes showed a greater resistance to the effects of x-rays than the ovaries. The testes of chicks irradiated with less than 200 r were similar to the testes irradiated during incubation.

The congestion in the blood vessels of the gonad could be demonstrated in more than 60 per cent of chicks irradiated, usually occurring more abundantly in the right testicle than in the left one. There were some instances in which one of the testicles showed extensive congestion while the other appeared normal.

Other signs of destruction were noted in chicks irradiated with dosages of x-rays above 200 r. The epithelium of the developing seminiferous tubules had reached a stage of retrogression that permitted a definite interpretation. The spermatogonia were totally inactive; the cytoplasm had a pale, "washed-out" appearance, and the nuclei were pyknotic. Mitotic activity could not be demonstrated. Owing to the relatively few tubules in the gonad, one would naturally conclude that degeneration of tubules must be taking place. However, unmistakable evidence for this assumption could not be found. It was quite apparent that the growth of the gonads was caused, not by the developing seminiferous tubules, but by the interstitial tissue. The latter was very abundant in every part of the testis (Fig. 7). The interstitial tissue was quite often seen organized into cord-like masses of cell surrounded by a definite connective capsule.

A peculiar case of melanin pigmentation in the interstitial tissue was observed in one irradiated chick. An attempt was made to repeat the anomaly, but without success: for this reason it is here described, not as a resultant of roentgen radiation but as a case of rare occurrence. Both testes appeared jet black in color when removed. Under the low power microscope it appeared as though the seminiferous tubules were roughly traced with India ink (Fig. 8). Under oil immersion the pigment was seen to consist of granules of various types, gathered into structures resembling chromatophores. There were no pigment granules in the seminiferous tubules, the structure of which appeared normal (Fig. 9).

*The Ovaries.*—A marked resistance of the ovary to x-rays was noted in chicks irradiated the first five days after hatching. The average ovary of this group may be characterized as an inactive structure in which cell division was seldom observed. Follicular degeneration was present but was limited in extent and number of specimen.

Beginning with the seventh day, the ovaries showed less resistance to x-rays of whatever dosage used: marked destruction of ovarian tissue was present in chicks that had received 400 r or more. In the more severely affected specimens, the ovary appeared to be in a hopeless stage of degeneration. The primary follicles might be entirely lacking or they might be present in small numbers: it was doubtful whether any of the latter could be called normal. They appeared pale in color as compared with adjacent connective tissue, and the cytoplasm had become vacuolated. The larger follicles persisted for a longer time but their disintegration was unmistakable.

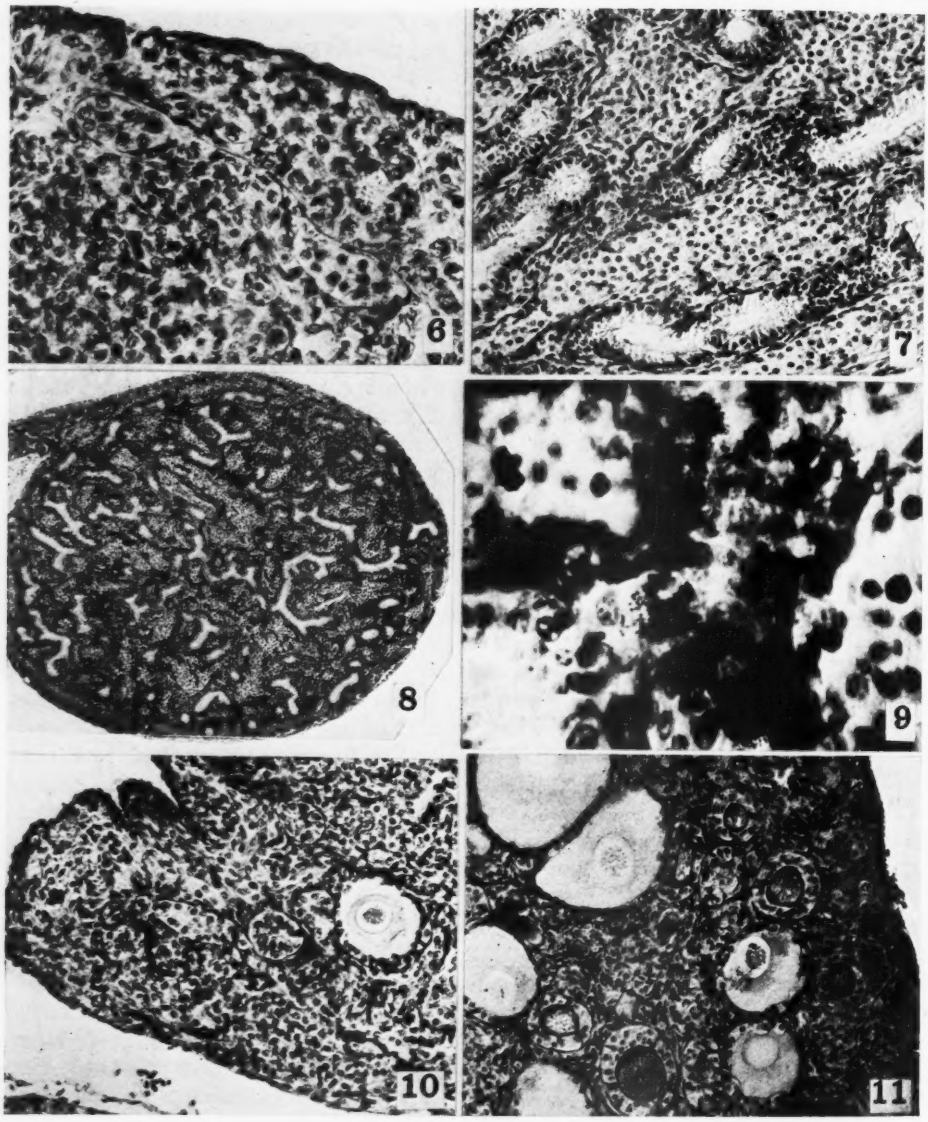


Fig. 6. Section of an ovary of a three-day-old chick x-rayed with 320 r on the sixth day of incubation. Note inactive germinal epithelium reduction of germ cells and the presence of cell-cords (×525).

Fig. 7. Section of a testis of a 21-day-old chick irradiated with 600 r on the second day after hatching. Note the abundance of interstitial tissue and the relatively few seminiferous tubules (×275).

Fig. 8. Section of a testis of a 14-day-old chick x-rayed on the seventh day after hatching with 480 r. Note distribution of pigment (×71).

Fig. 9. The same section as in Figure 8 (×1100).

Fig. 10. Section of an ovary of a 21-day-old chick irradiated on the seventh day after hatching with 400 r. Note atrophy of primary follicles and the abundance of cell-cords (×275).

Fig. 11. Section of an ovary of a 22-day-old chick irradiated on the twentieth day after hatching with 600 r. Note anovular and hemorrhagic follicles (×300).

The first step in the atrophying follicle was the loss of staining affinity; then the cytoplasm shrunk and became vacuolated. While the ovum atrophied, the granulosa proliferated cells that occupied the vacant space left by the degenerating ovum. In

the next stage the anovular follicle had the appearance of a solid, spherical mass of cells. However, this spherical body soon became an elongated, cord-like structure (Fig. 10).

If the chicks were killed and the ovaries fixed within 48 hours after irradiation, anovular follicles were common but the spaces of the destroyed ova were more often filled with blood than granulosa cells (Fig. 11). Initial stages of vacuolization of the cytoplasm of larger follicles were noticeable in these specimens.

Ovaries that have suffered extensive oocyte and follicle destruction invariably show large increase in interstitial cell content. Fibrosis of the cortex, particularly beneath the germinal epithelium, and vascular congestion were additional features commonly observed in these ovaries.

The ovaries irradiated with lower dosages (200 r or less) did not differ materially from those x-rayed during the first six days after hatching. At least some were found that were normal as far as could be diagnosed under the microscope.

### SUPERIMPOSED IRRADIATION

An attempt was made to ascertain the effects of double irradiation of the same specimen. The first application of x-rays was given during the incubation period and the second after hatching: altogether, 14 specimens were used for this purpose.

*The Testes.*—The superimposed dosages have added no new features to the picture of the testes, but the effects have been accentuated to such an extent that they could be recognized readily. Blood congestion was prevalent in this material. Totally sterile testes were found in specimens in which each of the two dosages were 200 r or more. The seminiferous tubules were abnormal in size, shape, and number. One and the same tubule may extend from one pole of the testis to the other pole. Abnormal enlargements and constrictions in the tubules were noted. Their number was found to be reduced to about one-half the normal in the right testis and approximately one-third in the left testis (Fig.12). The reductions seemed to be brought about by the degeneration of the partly differentiated seminiferous tubules. The cell masses, having great similarity to interstitial cells, were common in such testes, and at least some of them were enclosed in distinct connective tissue sheaths. However, a continuation between interstitial cell masses and degenerating seminiferous tubules was not established.

*The Ovaries.*—The findings for the ovaries were similar to those for the testes of this group. The observable anomalies were not new but represented summations of x-ray injuries that were noted, to a lesser extent, of course, in all the material studied.

In the ovaries with maximum injury in which the sum of the dosages was above 350 r, there were no normal follicles of any description. Anovular follicles and cell cords were the most outstanding features. Growing follicles, few in number and widely scattered, were found in some ovaries but they showed unmistakable signs of degeneration. The germinal epithelium was reduced to practically one layer of cells in thickness (Figs. 13 and 14).

The cell cords were, to all appearances, derived from the anovular follicles. The cell types of both structures were identical as far as could be discerned under the microscope. Anovular follicles developed into cell cords by elongation: they were always found in the ovarian cortex and usually close to the surface. These cords appeared to have grown rapidly, the larger ones always curved. In some parts of the ovary, the cortex was occupied mainly by cell cords and interstitial tissue (Fig. 15). After having gone through a certain amount of growth the constituent cell of the cords took a peripheral position and a lumen developed centrally. Such newly formed tubes have a marked resemblance to the seminiferous tubules of chicks at about the time of hatching. The developmental processes of the two structures were similar (Fig. 16).

Another male structure observed in the x-ray damaged ovary was the tunica

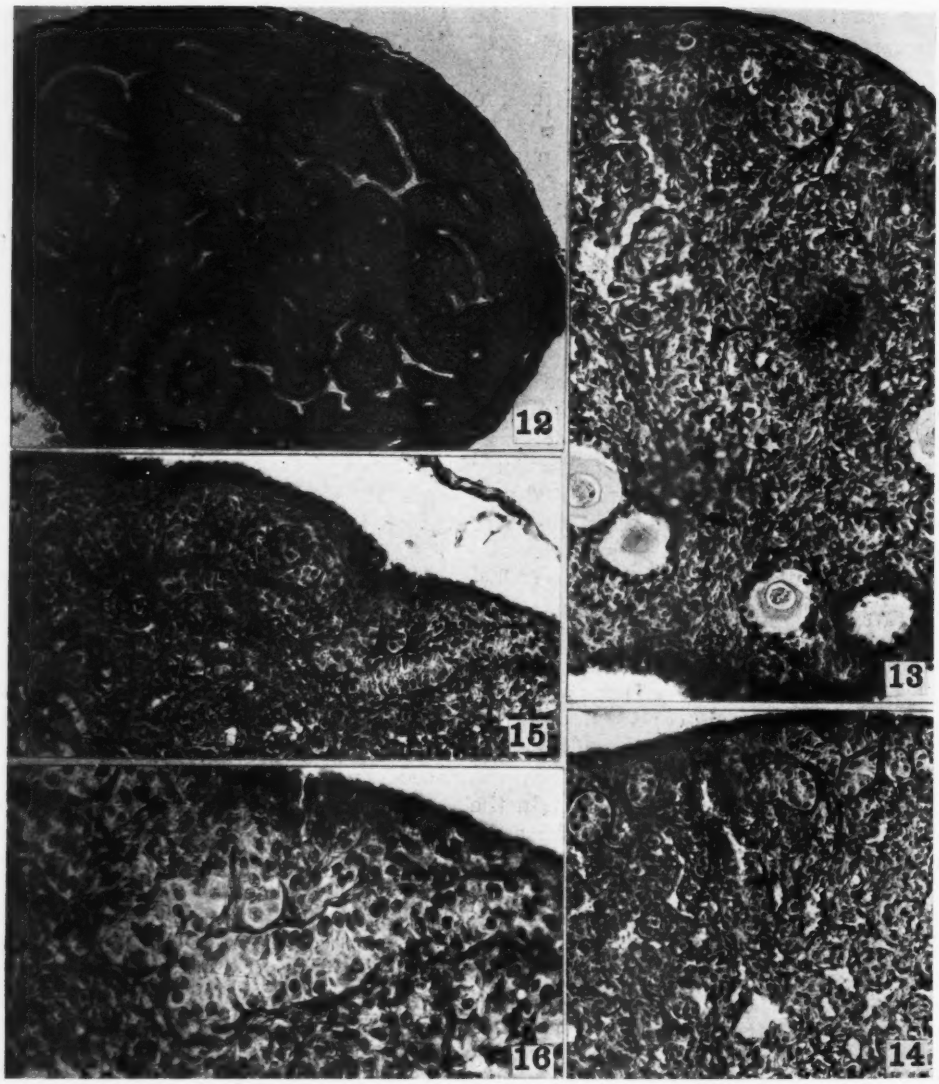


Fig. 12. Section of a testis of 25-day-old chick irradiated with 240 r at 70 hours' incubation and again on the seventh day after hatching with 240 r. Note the abundance of interstitial tissue and the reduction of seminiferous tubules (×89).

Fig. 13. Section through the upper pole of an ovary of a 25-day-old chick x-rayed with 240 r at 70 hours' incubation and again on the seventh day after hatching with 120 r. Note cell masses and cell-cords and degenerating follicles (×285).

Fig. 14. Section of the middle of the same ovary as in Figure 13. Note cell masses and cords (×275).

Fig. 15. Section through the lower pole of the same ovary as in Figure 13. Note cell masses, cords, tubules, and an exaggerated tunica albuginea (×275).

Fig. 16. Same section as in Figure 15 (×540).

albuginea (Figs. 3, 5, 13, and 15). In the normal ovary the tunica albuginea is very inconspicuous at any time of development or adult life: in the irradiated ovaries it was perhaps thicker than in the growing testes.

Well developed lymph nodes have been found in irradiated gonads, occurring most

commonly in ovaries of superimposed radiation. However, their occurrence was not directly related to age of the irradiated specimen nor to the dosage used.

X-ray effects on organs of the incubating chick other than the gonads have been noted in these experiments. The results were studied and described by the senior author (3).

## DISCUSSION

The effects of x-rays on mitotic activity have been noted in all of our experimental material. With small doses, 80 r or less, and with the present set-up of the x-ray machine, recovery takes place in a few hours. In dosages between 100 and 550 r, recovery is retarded, and with 600 r recovery seldom occurs. The latter is due to the fact that 600 r approximates very closely the lethal x-ray dose in the chick embryo. After the recovery from the initial effect, the mitotic activity shows retardation in dosages above 80 r and acceleration with dosages less than 80 r. Acceleration in the development of the chick has been reported by Gilman and Baetjer (6) and by Essenberg (2).

Marked resistance to the influence of x-rays was noticed in embryos irradiated before incubation and in chicks treated the first six days after hatching. In the first instance, the embryo was in an arrested stage of development; the metabolic and growth rates were low; thus, as would be expected, the injuries caused by x-rays were minor in character. We are inclined to assume that the same condition prevails in the second case. In chicks as in mammals, there is a drop in weight the first few days after birth, indicating a reduced growth rate.

It is now a well established fact that x-ray injuries vary directly with the dosage and with the age of the specimen. We have found it a guiding principle in all of the phases of our work. However, as was indicated above, exceptions to this rule have been noted. The more careful study of this problem was done by the senior author (3 and 5). It was found that the absorption of x-rays by the shell was a negligibly small factor, amounting to from 3.33 r to 6.66 r per 600 roentgen units. It was concluded that the "hereditary and environmental factors prior to laying play the major rôle."

With the present set-up of the machine and with the dosages varying from 40 to 600 r, the testes proved to be more resistant to the injuries of x-rays than the ovaries in every phase of the experiment. For an initial injury, involving an inhibition of mitosis, retrogressive changes in nucleus and cytoplasm of the spermatogonia, 200 r was required. For major injuries, involving the degeneration of the seminiferous tubules, from 300 to 600 r was required. In the ovaries, on the contrary, initial injuries were obtained with from 80 to 100 roentgen units. Injuries to the germinal epithelium, the primary follicles, and the formation of cell-cords resulted from dosages of 200 r. Major injuries, consisting of the destruction of primary and growing follicles and the formation of cell-cord tubules, appeared in dosages of 300 roentgen units.

The differential susceptibility to the effects of x-rays of the gonads of the two sexes is very likely due to more than one cause. We assume that the major cause is to be sought in the fact that the germ cells of the two sexes are at different levels of germ cell differentiation during the time of irradiation. In the ovary the germ cells go through developmental stages from oogonia to oocytes, primary follicles and growing follicles, whereas in the testes they seldom go beyond the spermatocyte stage.

The growth in size of the x-ray injured testes is not caused by the differentiation of the seminiferous tubules but by the increase of interstitial cells. The latter differ from interstitial cells of the controls by being segregated from the tubules and the testicular stroma by a rather definite connective tissue membrane. The cell structure of interstitial cells of the normal and the treated testes are identical as far as can be judged by inspection. It is possible that the ensheathed interstitial cell masses of the

x-ray injured testes originate from broken-down seminiferous tubules. It is also of interest to note that the right testis is invariably more susceptible to x-rays than the left one.

Probably the most peculiar findings of the entire experiment are the cell-cords of the ovaries injured by x-rays. They were noted in every phase of the experiment; the formation of the tubules was not, however, identified before the stage of superimposed irradiation. Most of the cell-cords seem to take origin from young follicles. They may, however, originate from germ cells that are in the process of follicle-formation, as indicated by the presence of cell-cords in ovaries in which primary follicles have not yet formed. At first they are spherical masses of cells ensheathed by a connective tissue membrane. Such structures were found most abundantly in ovaries that were irradiated during the time when primary follicles were in formation, *i.e.*, beginning from the sixth or seventh day after hatching. The cell-cords are produced by elongation of the spherical bodies. By rearrangement of the cells a lumen appears in the center. As stated before, the tubules resemble closely the developing seminiferous tubules of the normal male chick at the time of hatching. The developmental processes of the seminiferous and the cell-cord tubules are similar. The third male sign is the formation of an extensive tunica albuginea in the x-ray injured ovaries. It is possible that sex-inversion from the female to the male sex has taken place. However, further experimentation is needed before a definite statement can be made.

In comparing our results with those obtained by others (Hooker, 8; Snyder, 11; Murray, 10; Bagg and Little, 1), it would appear that the gonads of birds are more resistant to x-rays than those of mammals. Although these investigators have obtained injuries to testes and ovaries with much lower dosages, it is difficult, if not impossible, to correlate the erythema dose with that of the roentgen unit and the set-up of one machine with that of another. Allowing for individual variation, which is rather extensive, strict comparisons can be made only with the same set-up of the machine and with similar effects. One such comparison which has come out of this laboratory is available at the present time. Job, Leibold, and Fitzmaurice (9) showed that hydrocephalus can be induced in embryo rats at the ninth to eleventh day of pregnancy with a dosage averaging 52.5 r. The same effect was obtained in the chick embryo (3), at the average age of five and one-third days of incubation and an average dosage of 217 r.

## SUMMARY

In these experiments 121 specimens were used. Of these, 28 were controls, 18 eggs were radiated prior to incubation, 26 embryos were x-rayed at ages 5 to 12 days' incubation, and 49 chicks were treated to roentgen rays at ages 1 to 21 days post-hatching. Of those irradiated during incubation, 14 received a superimposed dosage after hatching. The dosage of x-rays varied from 40 to 600 r. The results are as follows:

(1) X-rays of any dosage effect the mitotic activity. Recovery is rapid with dosages 80 r or less; slow in dosages above 80 r; rare with a dosage of 600 r.

(2) Marked x-ray resistance was found to occur in embryos prior to incubation and in chicks during the first six days after hatching.

(3) Interference with mitotic activity and arrest of development of the ovary was caused by dosages above 80 r. Injuries to the germinal epithelium, the primary follicles, and the formation of cell-cords resulted from dosages 200 r and above. The destruction of follicles and the formation of tubules occurred in ovaries treated to 300 r or more.

(4) The testes showed a greater x-ray resistance than the ovaries. Initial injuries occurred in testes treated to 200 r. Major damages consisting of the degeneration of seminiferous tubules followed by increase of interstitial cells required above

300 r. The left testis proved to be more x-ray resistant than the right.

(5) In ovaries of major injury three apparently male characteristics were noted: The tubules resemble closely the seminiferous tubules of a young male chick; the process of formation of the seminiferous tubules and the tubules resulting from cell-cord are similar; a male tunica albuginea was formed in such ovaries. It is possible that sex reversal from female to male can be induced by x-rays.

(6) The gonads and the tissues of birds in general appear to be more x-ray resistant than those of mammals.

(7) Individual variation is much in evidence.

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# HOW X-RAYS MAY KILL CELLS[1]

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THE experimental work for this presentation was begun with the intention of studying a specific action of x-rays on cells that might account for their destruction by irradiation. While there have been many theories propounded to account for the lethal action of x-rays on cells, most of them are so generalized (*e.g.*, destruction of protoplasmic organization, injury to the nucleus or cytoplasm, increased permeability of plasma membrane, enzyme inactivation, protein precipitation, etc.) that they do not really explain why cells die when exposed to sufficient x-rays.

Before beginning our experiments we made a careful survey of the work done on the effects of radiation on cellular physiology. Most experiments with x-rays were directed toward a measurement of growth inhibition or cell death and comparatively few were aimed at determining radiation effects on specific metabolic processes of the cell. It seemed that respiration,[2] as a fundamental function of the cell, was capable of radiation injury; and that when the respiratory mechanism is interfered with serious derangement of other functions or death ensues (1).

Since a spectroscopic method of study of certain components of the cellular respiratory chain is convenient and sufficiently accurate, we elected to do our experimentation along this line. Yeast cells were chosen for the study for the following reasons:

1. With unicellular organisms the relative simplicity of cell mechanisms makes recovery from injury more difficult since there are no other cells to take over impaired functions. Recovery means the reconstruction of a lost function.

2. Small organisms are obviously necessary so that the energy received is essentially equal for all test objects.

3. The size of a sensitive zone, according to Holweck's (2) calculations based on the quantum hit-to-kill theory, approximates that of the yeast nucleus. Mayneord (3) has calculated a curve of probability of a cell five microns in diameter being traversed by an electron per unit of absorbed energy at various wave lengths (considering both photoelectrons and recoil electrons).

4. Yeast has a comparatively high rate of glycolysis; thus, it simulates a character of cancerous tissue.

5. The rapid multiplication and ease of culture enables one to deal with large numbers of individuals.

6. Its tested adequacy for cytochrome studies and its resistance to *p*H values so low as to be toxic to most cells, as well as the fact that extensive data relative to its metabolism have been accumulated which justify yeast's designation as the "Guinea pig of the biochemist."

Cellular respiration is carried on through reduction-oxidation reactions, the so-called "redox" systems. These reduction-oxidation reactions involve the virtual transfer of electrons. Water comprises the great bulk of protoplasm and a study of the action of x-rays on water is very illuminating. Risse (4) and Nurnberger (5) have shown that water becomes more acid and electrically is more conductive when irradiated; and Fricke (6) and others have shown that hydrogen and hydrogen peroxide are formed. Since redox systems are profoundly influenced by changes like these, it would be strange if the reduction-oxidation of the cells remained unaffected

[1] Presented before the Fifth International Congress of Radiology in Chicago, Sept. 16, 1937.

[2] The term "respiration" as used herein signifies all the energy-yielding reactions of the cell.

by irradiation. Further, as cellular damage resulting from x-rays shows a latent period and autocatalytic reactions likewise exhibit a preliminary lag phase, and since the so-called after-effect found in irradiated cells may also be exhibited by photochemical reactions, it seems logical to assume that the autocatalytic mechanisms governing the redox equilibria are affected by x-rays.

These catalysts function in maintaining a definite rate of cell metabolism and attempt to restore normal function when anything interferes with the cellular physiology. Since sudden changes in the respiratory needs of the cells cannot be met by sudden increase in those catalysts which are heavy metal complexes (*e.g.*, iron in cytochrome), secondary systems of catalysts are necessary to maintain activity of the primary ones. Co-catalysts are required for many reactions (*e.g.*, most glycolyses).

The primary catalysts of the cell's respiratory mechanism are the dehydrogenases, which activate hydrogen, and the oxidases, which activate oxygen. The bulk of cellular respiration is accomplished through the dehydrogenases and their co-catalysts. These complexes do not react directly with molecular oxygen but they do function with the intracellular hemes such as cytochrome through the flavoproteins. The co-catalyst portion of such a complex[3] transports hydrogen by the transformation of its pyridine nucleus to dihydropyridine. Such reduced co-catalysts are not autoxidizable but flavoprotein dehydrogenates them by itself becoming reduced to its leuco-form. The leuco-flavoproteins are oxidized through the cytochrome pigments. Nascent hydrogen by over-reduction of the co-catalyst causes irreversible inactivation, transforming the pyridine nucleus into a piperidine nucleus. Hydrogen peroxide also destroys or inactivates the co-catalyst which has been reduced physiologically.

The effect of x-irradiation on the redox system was studied by determining the time necessary for the reappearance of the cytochrome C absorption band in the visible spectrum following oxygenation. In brief, the following experiments were carried out (technical details of which will be reported elsewhere). A 7.5 per cent suspension of yeast, in phosphate buffer, was studied spectroscopically by trans-illuminating the yeast suspension with the light from a carbon arc. The cytochrome C line at 550 m$\mu$ was identified, verifying previously reported studies of others. The yeast suspension was then irradiated in a small flat-bottom dish and the cytochrome C absorption band was obliterated by bubbling oxygen through the yeast suspension. The disappearance of this cytochrome C band is the result of a temporary oxidation which changes the ferrous compound to ferric compound, the latter failing to show an absorption band at 550 m$\mu$. Functioning normally the dehydrogenases reduce the ferric to the ferrous form and the absorption band reappears within a comparatively short period of time. (Under our experimental conditions this time varied roughly from one to two and one-half minutes.) Thus the dehydrogenases re-established the normal redox equilibrium of the cell.

With x-ray dosages of from 3,000 to 6,000 r[4] (150 r/min. at 115 kv.p., 15 ma., 25 cm. distance and inherent tube filtration of from 3 to 4 mm. Al) the cytochrome C band did not reappear after oxygenation until from three and three-fourths to five and one-half minutes had elapsed, an average initial increase of 225 per cent. This we interpret as signifying definite although not irreparable damage to the dehydrogenase complex. The transitory nature of this effect indicates the ability of the injured cells to recover and but serves to emphasize the fundamental protoplasmic property of repair in the living organism. Since we used intact, living cells and util-

[3] The cozymase of yeast and Warburg's coenzyme are, respectively, di- and tri-phosphopyridine nucleotides; these function as co-catalysts.

[4] These are comparatively small dosages for yeast as the half lethal dose has been established as 42,000 r (7).

ized one component of the cellular redox chain as an indicator of the x-ray effect, this method permits direct, *in vivo* observation and measurement of the action of x-rays on intracellular metabolic processes. The method, without refinement, is not ideal as a quantitative procedure but it does adequately serve the purposes of this investigation; although the values obtained are not absolute values, the use of a control for each measurement and the duplication of individual peculiarities from experiment to experiment gave consistent results and comparable findings.

Correlating these facts with the proven ability of roentgen rays to produce both nascent hydrogen and hydrogen peroxide, we believe that the biological effects of x-rays on cells may result from inactivation or destruction of cell respiratory mechanisms through the effects of these substances on the co-catalysts of the dehydrogenases. Further, we believe that the cytochrome spectrum is an accurate indicator of this effect.

The wide distribution in nature (from yeast to man) of catalytic complexes containing pyridine nuclei as active components points to the fundamental rôle of such compounds in life processes. The formation by x-irradiation of the aqueous protoplasm, of hydrogen and hydrogen peroxide furnishes the means of inactivation or destruction of this active group so essential to the functioning of the fundamentally important systems of which they are a part. Among the well-authenticated and established effects of x-ray action on living cells the following are, we believe, adequately explained by the above reactions. Likewise they furnish criteria upon which the usefulness of any hypothesis of x-ray action on cells may be judged.

1. The differential susceptibility of different kinds of cells and tissues to x-rays and the increased susceptibility of young or rapidly growing cells seems very definitely connected with their higher metabolic rate and increased water content. The higher the metabolic rate, the greater the sensitivity. The more active respiratory mechanism required by such cells renders them especially sensitive to damage such as we have described.

2. The ability of an irradiated cell to recover from sub-lethal exposure to x-rays is to be found in its ability to elaborate more catalyst to replace that which was inactivated, and to do it rapidly enough to meet its own particular respiratory requirements.

3. The cumulative effect of divided small doses depends upon a time spacing less than that required by the cell to elaborate enough catalyst to completely replace the inactivated catalyst.

4. The delayed lethal action of x-rays on cells (latent period) finds explanation in the fact that the reaction chain involved contains auto-catalysts.

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# CASE REPORTS AND NEW DEVICES

## THE USE OF AQUAPHOR IN IRRADIATION EPIDERMITIS

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When Coutard, in 1932, introduced his method of protracted fractional irradiation he advocated doses which by reason of their intensity, produced severe reactions on the skin. These were manifested successively by erythema, increased pigmentation and blistering, but as the quantity of x-rays was administered in fractions, complete healing of the skin followed. In the technic as advocated by Coutard the skin reaction appears about the sixteenth to the twenty-first day, progresses to blistering and persists for about 14 to 21 days.

This therapeutic procedure is at the present time quite generally employed but many therapists utilize modifications of Coutard's original technic, with treatments administered to the stage of skin denudation. Subsequent reaction is of considerable discomfort to the patient because of the burning, weeping, angry red effect. Moreover, this does not permit the concurrent use of interstitial radium therapy for residual metastatic glands, should the plan of treatment call for this.

In the Radiation Therapy Service at Bellevue Hospital we employ both the regular Coutard technic, and also the modifications thereof, in which doses are given to the stage of skin destruction. For the past several years, we have used innumerable types of ointments and solutions, the formulas for which either originated with us or were suggested in the literature. Among these were solutions of boric acid, azochloramid, caroid, sea water, bland ointments such as zinc oxide, boric acid, yellow oxide of mercury, radolatum, joncolia, borofax, vaseline, nupercaine, and alvagel (made from aloes vera leaf), etc. None of these substances, however, gave any noteworthy relief from the burning pain or lessened the time required for healing the radiation skin reaction.

Having long noticed that excessive weeping in a radiation epidermitis was a constant finding, we engaged in an intensive search for a bland ointment capable of combating this serous oozing, and thus chanced upon Aquaphor.[1]

Aquaphor is cholesterolized petrolatum. It has an absorption base containing as the active hydrophyllic ingredient, 6 per cent of a group of esters of cholesterols in an aliphatic hydrocarbon base. It appears as a pale yellow, semisolid, odorless unguent that is neutral in reaction and has the property of absorbing at least 200 per cent water by weight. Aquaphor mixes well with fatty and aqueous excretions of the skin; it spreads easily and melts at body skin temperature.

In using, the ointment is applied in a thin film directly over the reactive area, preferably without any gauze bandage. To the patient the relief from burning is immediate and lasting; objectively, healing is hastened by days. The most convincing proof of the superior efficacy of this ointment appeared when Aquaphor was used as a regular routine in the care of patients treated with protracted irradiation. These patients volunteered the opinion that they had obtained greater relief from the new ointment than from any other theretofore used.

After an observation of a very large number of cases treated with Aquaphor, we have noted that this ointment is somewhat caustic to the normal skin because of its hygroscopic property. Therefore, we recommend that caution be employed and that the ointment be applied as closely as possible within the confines of the treated area.

To date, Aquaphor has, in our opinion, proven the most efficient remedy in combating the burning pain of radiation effects on the skin.

[1] Aquaphor was supplied for these clinical tests through the courtesy of the manufacturers, the Duke Laboratories, Long Island City, New York.

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## ONE AND ONE-HALF YEARS' EXPERIENCE IN THE EMPLOYMENT OF 220 KILOVOLTS X-RAY THERAPY WITH HEAVY FILTER

### REPORT ON SEVEN CASES OF CARCINOMA OF THE BLADDER

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For thirteen years prior to April, 1936, we had employed 200 kv. x-ray therapy with 0.5 mm. Cu filter in the treatment of cancer. At that time we began using a Westinghouse Pulsating X-ray Therapy Machine, 220 kv., 20 ma., 50 cm. T.S.D., with filter consisting of 0.77 mm. Sn plus 0.25 mm. Cu plus 1 mm. Al, H.V.L. 2.55 mm. Cu, equivalent on a quality basis to 3.75 mm. Cu.

We have been very much gratified with the improvement in results obtained by this method, in all types of cancer located deep within the body, as compared with our former method of treatment.

From July, 1936, to March, 1937, we treated seven cases of carcinoma of the bladder, in all of which we had histologic diagnosis.

### CASE REPORTS

Case 1. J. B. J., white male, aged 56 years; referred by the Crowell Clinic. He gave a history of hematuria for two months. A papillary tumor was found in the bladder and as much of it as possible was removed by the resectoscope.

The pathologist's report was papillary epithelial neoplasm showing solid medullary extensions at base. Treating the papillary carcinoma, the patient was given a total of 9,000 r to the pelvis through five 15 × 15 cm. skin portals, in doses of from 225 to 300 r over a period of 57 days. On the twenty-eighth day there was extensive hemorrhage from the bladder and it was necessary to suspend treatment for two weeks. The patient is clinically and cystoscopically well 16 months after treatment.

Case 2. S. J. L., white male, aged 65 years; referred by the Crowell Clinic. History of hematuria for three weeks. The cystoscopist found an infiltrating tumor in the bladder and removed a part of it by the resectoscope. The tissue showed epidermoid carcinoma. A total dose of 9,000 r was given to the pelvis through five skin portals 15 × 15 cm. in size. The treatment was given over a period of 51 days, 225 r being given at each treatment. The patient is carrying on his work as a farmer but will not report for observation. It has been 16 months since he was treated.

Case 3. J. R. W., white male, aged 65, referred by Dr. McKay and associate. He gave a history of two hemorrhages from the bladder within a month. On cystoscopy by Dr. H. W. McKay, a small papillary tumor was found in the bladder and removed by the resectoscope, after which the base was fulgurated. The tissue showed malignant papilloma. A total of 9,000 r was given to the pelvis through four 15 × 15 cm. skin portals over a period of 46 days. One area was treated each day with 225 r. Fourteen months after treatment cystoscopy reveals no newgrowth in the bladder and there is no evidence of metastasis.

Case 4. B. H. G., white male, aged 65 years, referred by the Crowell Clinic. There was a history of resection of a benign hypertrophied prostate three years before, frequent hematuria during the intervening years. Five weeks before reporting to the Crowell Clinic he had complete obstruction. There was great enlargement of the prostate, with some nodules projecting into the bladder. Perineal prostatectomy was done and the tissue was studied by Dr. L. C. Todd, with the following findings: "Benign adenomatous hypertrophy of the prostate. There is an infiltrating epithelial neoplasm derived from the bladder mucosa which has extended into the base and up into the matrix of one of the intravesical nodes, producing necrosis with secondary softening and hemorrhage. Carcinoma of the bladder wall infiltrating the prostate. High degree of malignancy." The patient was given 10,000 r to the pelvis in doses of 225 r each, through six 15 × 15 cm. portals. The total dose was given in a period of 51 days. The patient is clinically and cystoscopically well eleven months after treatment.

Case 5. Mrs. H. A. G., white female, aged fifty years, referred by the Crowell Clinic. For five months she had hematuria at frequent intervals. There were three small tumors in the bladder; of these, one was 1 cm. in diameter and two about 3 mm. in diameter each. Biopsy was done and the tumors fulgurated. The material was found to be papillary carcinoma of a high degree of malignancy. A total of 11,000 r was given to the pelvis through five 15 × 15 cm. skin portals in doses of 225 r. In nine months she had recurrence of the cancer in the bladder. She is being treated with x-rays (220 kv., 15 ma., 100 cm. distance, Thoraeus filter, 0.462 Sn) twice daily, 150 r at each treatment.

Case 6. F. R. U., white male, aged 57 years, referred by the Crowell Clinic. He gave a history of hematuria of four months' duration: no pain and no obstruction: there was a large tumor in the right side of the bladder and the prostate was enlarged. A part of the tumor and of the prostate were removed by the resectoscope; in all, three grams of tissue were removed. The pathologist's report was as follows: "The specimen consists largely of muscular elements and in one area near the bladder mucosa shows a deep infiltration of transitional carcinoma presenting in its deeper portions a high degree of malignancy. Carcinoma of the bladder (malignancy Grade 4)." Over a period of 57 days a total of 11,250 r was given to the pelvis through five portals, 15 × 15 cm. each. The daily dose was 225 r to one area. Four months later the patient had hematuria. He was cystoscoped and the bleeding point was fulgurated. Biopsy was done at this time and the material showed carcinoma (Grade 4). The patient is living eight months after treatment, but has residual cancer in the bladder.

Case 7. F. S. W., white male, aged 41 years, referred by the Crowell Clinic. He had hematuria for nine months and there was severe pain in the bladder region. There was a tumor 2.5 × 2.5 × 2.5 cm. in the right anterior part of the bladder. Biopsy material showed squamous-cell carcinoma (Grade 3).

There was infiltration of the muscle. Treatment was begun and 6,345 r was given to the pelvis in 32 days. At that time the pain in the bladder region was so severe that it was necessary to suspend treatment. Cystoscopy revealed that the tumor had grown rapidly while receiving x-ray treatment. The patient died four months after treatment was begun. At autopsy it was found that the tumor had invaded about half of the bladder wall and it almost filled the bladder cavity.

The doses reported in all the cases are of r measured in air.

Three of these patients had papillary carcinoma, while four had the infiltrating type. Two of the three papillary tumors showed good response to the treatment, while one of them recurred in nine months. Two of the infiltrating tumors have shown good response to the treatment, while two did not show satisfactory response.

Of the seven patients, six are living from eight to sixteen months. Two have residual malignant disease in the bladder, and one of these (Case 5, a papillary tumor) is now having x-ray treatment for the second time. One, a farmer, is carrying on his work but refuses to come in for cystoscopic observation, though, so far as we can determine, a good result was obtained. In three of the cases we have cystoscopic evidence that the tumor was completely destroyed and that there has, as yet, been no recurrence.

On account of improvement in results with this method of treatment, we are now employing 220 kv. constant potential and using 6 mm. Cu filter (equivalent) in the treatment of tumors in the deeper structures. With the greater filtration we believe that the results will be proportionately improved.

We are fully cognizant of the fact that this small series of cases, the results obtained in them, and the short time since they were treated do not constitute sufficient evidence from which to draw any positive conclusion. However, the improvement in immediate results from methods employed in these cases encourages us to believe that there will be improvement in final results as compared with those obtained by former methods of treatment.

### ADDENDUM

Six months have elapsed between the time this paper was written and its publication.

Case 1. This individual is still living and well 22 months after treatment; Case 2, 22 months; Case 3, 20 months; Case 4, 17 months.

Case 5. Mrs. H. A. G. had recurrence nine months after treatment. This tumor was fulgurated and she was given a second series of treatments with the following factors: 100 cm. distance, 220 kv., 15 ma., Thoraeus filter equivalent to 2 mm. copper. A total of 5,230 r was given to each of four areas—one anterior, one posterior, and one to each side of the pelvis. The patient is now, 17 months after beginning treatment the first time, clinically well and cystoscopically free from tumor.

Case 6 had a recurrence four months after treatment and lived a total of twelve months.

# RADIOLOGICAL SOCIETIES IN THE UNITED STATES

*Editor's Note.*—Will secretaries of societies please cooperate with the Editor by supplying him with information for this section. Please send such information to Leon J. Menville, M.D., 1201 Maison Blanche Bldg., New Orleans, La.

CALIFORNIA

*California Medical Association, Section on Radiology.—Chairman,* John D. Lawson, M.D., 1306 California State Bldg., Sacramento; *Secretary,* Karl M. Bonoff, M.D., 1930 Wilshire Blvd., Los Angeles. Meets annually with California Medical Association.

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*Los Angeles County Medical Association, Radiological Section.—President,* John F. Chapman, M.D., 65 N. Madison Ave., Pasadena; *Vice-president,* E. N. Liljedahl, M.D., 1241 Shatto St.; *Secretary,* Merl L. Pindell, M.D., 678 South Ferris Ave.; *Treasurer,* Henry Snure, M.D., 1414 Hope Street. Meets every second Wednesday of month at County Society Building.

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*Pacific Roentgen Club.—Chairman,* Raymond G. Taylor, M.D., 1212 Shatto St., Los Angeles; *Secretary,* L. Henry Garland, M.D., 450 Sutter St., San Francisco.

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*San Francisco Radiological Society.—Secretary,* L. H. Garland, M.D., 450 Sutter Street. Meets monthly on first Monday at 7:45 P.M., alternately at Toland Hall and Lane Hall.

COLORADO

*Denver Radiological Club.—President,* John S. Bouslog, M.D., 246 Metropolitan Bldg.; *Vice-president,* Sanford Withers, M.D., 304 Republic Bldg.; *Secretary,* Ernst A. Schmidt, M.D., Colorado General Hospital; *Treasurer,* H. P. Brandenburg, M.D., 155 Metropolitan Bldg. Meets third Tuesday of each month at homes of members.

CONNECTICUT

*Connecticut State Medical Society, Section on Radiology.—Chairman,* Kenneth K. Kinney, M.D., 29 North Street, Willimantic; *Vice-chairman,* Francis M. Dunn, M.D., 100 State Street, New London; *Secretary-Treasurer,* Max Climan, M.D., 242 Trumbull St., Hartford. Meetings twice annually in May and September.

DELAWARE

Affiliated with Philadelphia Roentgen Ray Society.

FLORIDA

*Florida State Radiological Society.—President,* H. O. Brown, M.D., 404 First National Bank Bldg., Tampa; *Vice-president,* H. B. McEuen, M.D., 126 W. Adams St., Jacksonville; *Secretary-Treasurer,* J. H. Lucinian, M.D., 168 S. E. 1st St., Miami.

GEORGIA

*Georgia Radiological Society.—President,* James J. Clark, M.D., Doctors Bldg., Atlanta; *Vice-president,* William F. Lake, M. D., Medical Arts Bldg., Atlanta; *Secretary-Treasurer,* Robert C. Pendergrass, M.D., Prather Clinic, Americus. Meetings twice annually, in November and at the annual meeting of the Medical Association of Georgia in the spring.

ILLINOIS

*Chicago Roentgen Society.—President,* David S. Beilin, M.D., 411 Garfield Ave.; *Vice-president,* Chester J. Challenger, M.D., 3117 Logan Blvd.; *Secretary-Treasurer,* Roe J. Maier, M.D., 7752 Halsted St. Meets second Thursday of each month, September to May, except December.

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*Illinois Radiological Society.—President,* Cesare Gianturco, M.D., 602 W. University Ave., Urbana; *Vice-president,* Fred H. Decker, M.D., 802-Peoria Life Bldg., Peoria; *Secretary-Treasurer,* Edmund P. Halley, M.D., 968 Citizens Bldg., Decatur. Meetings quarterly by announcement.

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*Illinois State Medical Society, Section of Radiology.—President,* Roswell T. Pettit, M.D., 728 Columbus St., Ottawa; *Secretary,* Ralph G. Willy, M.D., 1138 N. Leavitt St., Chicago.

INDIANA

*Indiana Roentgen Society.—President,* Stanley Clark, M.D., 108 N. Main St., South Bend; *President-elect,* Juan Rodriguez, M.D., 2903 Fairfield Ave., Fort Wayne; *Vice-president,* A. C. Holley, M.D., Attica; *Secretary-Treasurer,* Clifford C. Taylor, M.D., 23 E. Ohio St., Indianapolis. Annual meeting in May.

IOWA

*The Iowa X-ray Club.*—Holds luncheon and business meeting during annual session of Iowa State Medical Society.

MAINE

*See* New England Roentgen Ray Society.

MARYLAND

*Baltimore City Medical Society, Radiological Section.—Chairman,* Marcus Ostro, M.D., 1810 Eutaw Place; *Secretary,* H. E. Wright, M.D., 101 W. Read St., Baltimore. Meetings second Tuesday of each month.

MASSACHUSETTS

*See* New England Roentgen Ray Society.

MICHIGAN

*Detroit X-ray and Radium Society.—President,* E. W. Hall, M.D., 10 Peterboro Street; *Vice-president,*

Sam W. Donaldson, M.D., 326 North Ingalls St., Ann Arbor; *Secretary-Treasurer*, E. R. Witwer, M.D., Harper Hospital. Meetings first Thursday of each month from October to May, inclusive, at Wayne County Medical Society Bldg.

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*Michigan Association of Roentgenologists.—President*, E. R. Witwer, M.D., Harper Hospital, Detroit; *Vice-president*, D. W. Patterson, M.D., 622 Huron Street, Port Huron; *Secretary-Treasurer*, C. K. Hasley, M.D., 1429 David Whitney Bldg., Detroit.

MINNESOTA

*Minnesota Radiological Society.—President*, Walter H. Ude, M.D., 78 S. 9th St., Minneapolis; *Vice-president*, Leo G. Rigler, M.D., University Hospitals, Minneapolis; *Secretary-Treasurer*, Harry Weber, M.D., 102 Second Ave., S. W., Rochester. Meetings quarterly.

MISSOURI

*The Kansas City Radiological Society.—President*, L. G. Allen, M.D., 907 N. 7th St., Kansas City, Mo.; *Secretary*, Ira H. Lockwood, M.D., 306 E. 12th St., Kansas City, Mo. Meetings last Thursday of each month.

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*The St. Louis Society of Radiologists.—President*, Joseph C. Peden, M.D., 634 N. Grand Blvd.; *Secretary*, W. K. Mueller, M.D., 607 N. Grand Blvd. Meetings fourth Wednesday of each month.

NEBRASKA

*Nebraska Radiological Society.—President*, E. W. Rowe, M.D., 128 N. 13th St., Lincoln; *Secretary*, D. Arnold Dowell, M.D., 117 S. 17th St., Omaha. Meetings first Wednesday of each month at 6 P.M. in Omaha or Lincoln.

NEW ENGLAND ROENTGEN RAY SOCIETY

(Maine, New Hampshire, Vermont, Massachusetts, and Rhode Island.) *President*, Frank E. Wheatley, M.D., 520 Beacon St., Boston; *Secretary*, E. C. Vogt, M.D., 300 Longwood Ave., Boston. Meetings third Friday of each month from October to May, inclusive, usually at Boston Medical Library.

NEW HAMPSHIRE

*See* New England Roentgen Ray Society.

NEW JERSEY

*Radiological Society of New Jersey.—President*, Milton Friedman, M.D., Newark Beth Israel Hospital, Newark; *Vice-president*, P. S. Avery, M.D., 546 Central Ave., Bound Brook; *Secretary*, W. James Marquis, M.D., 198 Clinton Ave., Newark; *Treasurer*, James Boyes, M.D. ,744 Watchung Ave., Plainfield. Meetings at Atlantic City at time of State Medical Society, and Midwinter in Newark as called by president.

NEW YORK

*Brooklyn Roentgen Society.—President*, Albert Voltz, M.D., 115–120 Myrtle Avenue, Richmond Hill; *Vice-president*, A. L. L. Bell, M.D., Long Island College Hospital, Henry, Pacific, and Amity Sts., Brooklyn; *Secretary-Treasurer*, E. Mendelson, M.D., 132 Parkside Ave., Brooklyn. Meetings first Tuesday in each month at place designated by president.

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*Buffalo Radiological Society.—President*, Walter Mattick, M.D., 101 High St.; *Vice-president*, Chester Moses, M.D., 333 Linwood Ave.; *Secretary-Treasurer*, J. S. Gian-Franceschi, M.D., 610 Niagara Street. Meetings second Monday evening each month.

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*Central New York Roentgen-ray Society.—President*, W. E. Achilles, M.D., 60 Seneca St., Geneva; *Vice-president*, M. T. Powers, M.D., 250 Genesee St., Utica; *Secretary-Treasurer*, Carlton F. Potter, M.D., 425 Waverly Ave., Syracuse. Meetings held in January, May, and October as called by Executive Committee.

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*Long Island Radiological Society.—President*, David E. Ehrlich, M.D., 27 W. 86th St., New York City; *Vice-president*, H. Koiransky, M.D., 43–37 47th St., Long Island City; *Secretary*, S. Schenck, M.D., 115 Eastern Parkway, Brooklyn; *Treasurer*, Moses Goodman, M.D., 45–01 Skillman Ave., Long Island City. Meetings fourth Thursday evening each month at Kings County Medical Bldg.

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*New York Roentgen Society.—President*, Raymond Lewis, M.D., 115 E. 61st St., New York City; *Vice-president*, Henry K. Taylor, M.D., 667 Madison Ave., New York City; *Secretary*, Roy D. Duckworth, M.D., 170 Maple Ave., White Plains; *Treasurer*, Eric Ryan, M.D., St. Luke's Hospital, New York City; *Member of Executive Committee*, E. Forrest Merrill, M.D., 30 W. 59th St., New York City. Meetings third Monday evening each month at Academy of Medicine.

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*Rochester Roentgen-ray Society.—Chairman*, Joseph H. Green, M.D., 277 Alexander St.; *Secretary*, S. C. Davidson, M.D., 277 Alexander St. Meetings at convenience of committee.

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*Society of Radiological Economics of New York.—President*, Albert L. Voltz, M.D., 115–120 Myrtle Ave., Richmond Hill; *Vice-president*, M. M. Pomeranz, M.D., 911 Park Ave., New York City; *Secretary*, W. F. Francis, M.D.; *Treasurer*, Theodore West, M.D., United Hospital, Port Chester. Meetings first Monday evening each month at McAlpin Hotel.

NORTH CAROLINA

*Radiological Society of North Carolina.—President*, Robert P. Noble, M.D., 127 W. Hargett St., Raleigh; *Vice-president*, A. L. Daughtridge, M.D., 144 Coast Line St., Rocky Mount; *Secretary-Treasurer*, Major I. Fleming, M.D., 404 Falls Road, Rocky Mount. Meetings with State meeting in May, and meeting in October.

OHIO

*Cleveland Radiological Society.*—*President,* North W. Shetter, M.D., Lakewood City Hospital, Lakewood; *Vice-president,* John Heberding, M.D., St. Elizabeth's Hospital, Youngstown; *Secretary-Treasurer,* Harry Hauser, M.D., Cleveland City Hospital, Cleveland. Meetings at 6:30 P.M. at Cleveland Chamber of Commerce Club on fourth Monday of each month from October to April, inclusive.

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*Radiological Society of the Academy of Medicine* (Cincinnati Roentgenologists).—*President,* B. M. Warne, M.D., Doctors Building, Cincinnati; *Secretary-Treasurer,* Justin E. McCarthy, M.D., 707 Race St., Cincinnati, Ohio. Meetings held third Tuesday of each month.

PENNSYLVANIA

*Pennsylvania Radiological Society.*—*President,* Charles S. Caldwell, M.D., 520 S. Aiken, Ave., Pittsburgh; *First Vice-president,* Thomas L. Smyth, M.D., 111 N. 8th St., Allentown; *Second Vice-president,* Reuben G. Alley, M.D., Western Pennsylvania Hospital, Pittsburgh; *Secretary-Treasurer,* Lloyd E. Wurster, M.D., 416 Pine St., Williamsport; *President-elect,* Louis A. Milkman, M.D., 212 Medical Arts Bldg., Scranton; *Editor,* William E. Reiley, M.D., Clearfield. Annual meeting, May, 1939. Exact date and place to be decided.

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*Philadelphia Roentgen Ray Society.*—*President,* Thomas P. Laughery, M.D., Germantown Hospital; *Vice-president,* Elwood E. Downs, M.D., Jeans Hospital, Fox Chase; *Secretary,* Barton H. Young, M.D., Temple University Hospital; *Treasurer,* R. Manges Smith, M.D., Jefferson Hospital. Meetings first Thursday of each month from October to May, Thompson Hall, College of Physicians, 19 S. 22nd St., 8:15 P.M.

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*The Pittsburgh Roentgen Society.*—*President,* William B. Ray, M.D., 320 E. North Avenue, N. S. Pittsburgh; *Secretary,* Harold W. Jacox, M.D., 4800 Friendship Ave. Meetings held second Wednesday of each month at 4:30 P.M., from October to June at various hospitals designated by program committee.

RHODE ISLAND

*See* New England Roentgen Ray Society.

SOUTH CAROLINA

*South Carolina X-ray Society.*—*President,* Robert B. Taft, M.D., 105 Rutledge Ave., Charleston; *Secretary-Treasurer,* Hillyer Rudisill, M.D., Roper Hospital, Charleston. Meetings in Charleston on first Thursday in November, also at time and place of South Carolina State Medical Association.

SOUTH DAKOTA

Meets with Minnesota Radiological Society.

TENNESSEE

*Memphis Roentgen Club.*—Chairmanship rotates monthly in alphabetical order. Meetings second Tuesday of each month at University Center.

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*Tennessee State Radiological Society.*—*President,* S. S. Marchbanks, M.D., 508 Medical Arts Bldg., Chattanooga; *Vice-president,* Steve W. Coley, M.D., Methodist Hospital, Memphis; *Secretary-Treasurer,* Franklin B. Bogart, M.D., 311 Medical Arts Bldg., Chattanooga. Meeting annually with State Medical Society in April.

TEXAS

*Texas Radiological Society.*—*President,* R. G. Giles, M.D., Medical Arts Bldg., San Antonio; *President-elect,* Jerome H. Smith, M.D., Shannon West Texas Memorial Hospital, San Angelo; *First Vice-president,* C. F. Crain, M.D., 416 Chaparral St., Corpus Christi; *Second Vice-president,* M. H. Glover, M.D., 904 8th St., Wichita Falls; *Secretary-Treasurer,* G. D. Carlson, M.D., 3121 Bryan St., Dallas. Meets annually. San Antonio is place of meeting, Oct. 22, 1938.

VERMONT

*See* New England Roentgen Ray Society.

VIRGINIA

*Radiological Society of Virginia.*—*President,* Fred M. Hodges, M.D., 100 W. Franklin St., Richmond; *Vice-president,* L. F. Magruder, M.D., Raleigh and College Aves., Norfolk; *Secretary,* V. W. Archer, M.D., University of Virginia Hospital, Charlottesville.

WASHINGTON

*Washington State Radiological Society.*—*President,* H. E. Nichols, M.D., Stimson Bldg., Seattle; *Secretary,* T. T. Dawson, M.D., Fourth and Pike Bldg., Seattle. Meetings fourth Monday of each month at College Club.

WISCONSIN

*Milwaukee Roentgen Ray Society.*—*Secretary,* S. A. Morton, M.D., Columbia Hospital, Milwaukee. Meets monthly on first Friday.

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*Radiological Section of the Wisconsin State Medical Society.*—*Secretary,* Russel F. Wilson, M.D., Beloit Municipal Hospital, Beloit. Two-day annual meeting in May and one day in connection with annual meeting of State Medical Society, in September.

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*University of Wisconsin Radiological Conference.*—*Secretary,* E. A. Pohle, M.D., 1300 University Ave., Madison, Wis. Meets every Thursday from 4 to 5 P.M., Room 301, Service Memorial Institute.

# EDITORIAL

LEON J. MENVILLE, M.D., *Editor* HOWARD P. DOUB, M.D., *Associate Editor*

## IS A ROENTGENOLOGIST A DOCTOR?

The radiologist has his own peculiar trials and tribulations and occasionally he boils over and writes about them to the editor. The following letter will strike a sympathetic chord in the breast of many a radiologist.

During the past ten years I have listened to considerable discussion regarding the forces which menace the existence of roentgenologists. There is the hospital with its capitalistic yen for group insurance. There is the competition of the lay "x-ray specialist" which, I understand, has been legitimated in some States. A condition, however, which impresses me as being a still greater menace hereabouts has received comparatively little attention. I refer to the attitude of the practising physician himself on whom the roentgenologist must depend for referred work.

I have practised roentgenology for ten years in a Western city of 140,000 population, the medical personnel of which is somewhat mixed as to standards. We have a part-time medical school which necessitates the completing of a medical course elsewhere and this situation tends to varying attitudes in the routine handling of patients. We have also a fairly large representation of the all-sufficient type of country practitioner turned urban who cordially hates the thought of referring his patient to any specialist for any consideration.

My reason for doubting if, in the eyes of the average practitioner—and naturally, therefore, in the eyes of his patients—the roentgenologist is a doctor is based on the impression fostered by the remarks and comments I have heard from day to day. More and more patients enter my office with the unflattering request, "Dr. So-and-so told me to come here and have you make a picture and he will call and see it to-morrow." And later, "Why do you charge so much more than they charge for other pictures?" And, "I simply can't understand why I should have to pay for a picture and then let you keep it yourself."....etc., *ad nauseum*.

Such remarks are too often a reflection of the comments of the patient's physician. And then there is the little drama of "showing the patient his trouble on the film." Recently a prominent medical journal has been displaying among its advertising columns an appealing cut of a prosperously rotund internist pointing out things on the x-ray plate to his patient. The inference is, "Here is your trouble, Madam. I fear we must resort to surgery." The idea the advertisers very cleverly put over is, "Doctor, you can sell bigger and better operations if you use Blanko Films." I have witnessed this little drama many times of late and listened to accompanying sales talk. Needless to say, it reduces the x-ray specialist to a rather inferior position.

On the staff of the hospital where I have headed the x-ray department for nearly a decade are ten or fifteen loyal friends who, in pathological conferences or staff meetings will rise and say: "Dr. X, of the X-ray Department, will tell us something about the findings in this case and discuss the films." On the other hand, I frequently sit and fume with indignation while some nice new intern or one of the forty other staff members announces, "We had some pictures made and they didn't seem to show much. They're here if anyone cares to look them over."

Now these observations are not, as the reader may suspect, an indication of either wounded professional vanity, financial disappointment, or paranoid tendencies on the part of the author. They are honestly cited as an indication of a general attitude among the medical profession. It is my sincere opinion that in this locality, and probably in others similarly situated, a technical specialist does not obtain the degree of professional respect due a man

with an M.D. degree. Possibly in cities of this size the research or technical side of medicine occupies a relatively unimportant position. Undoubtedly, the salesman from the big manufacturing concerns does much in the way of spreading false doctrine to the effect that anyone can do x-ray work. Certain specialists, notably the urologist, the oto-laryngologist, and the orthopedist, have become proficient in the use of x-ray as regards their particular fields. The tendency therefrom is not favorable to the roentgenologist. It also occurs to me at times that just possibly we are overstocked with specialists in the United States. It might be a good idea to bow to public psychology and set up a new professional classification by which the title "Dr." is reserved for only the most erudite of internists and surgeons.

I see no immediate remedy for this apparent lack of prestige on the part of technical medicine; neither do I think that total absorption of the specialty of roentgenology will take place as has been suggested. One conclusion, however, is obvious: The trustees of a hospital with their unrelenting interest in financial advantages are sure to interpret this attitude of staff members in general as a signal to go ahead and place the x-ray laboratory on a clock-punching basis. This has already been done in some hospitals and will undoubtedly progress until the general practitioner takes a definite stand to the contrary.

Q. B. CORAY, M.D.

Many radiologists, both young and old, will sympathize with the writer of the above letter because all have to contend with the same problem to a greater or lesser degree. May we point out, without any inclination to preach, that the cure for this problem, like many others which the radiologist must solve, is in his own hands. It is true that it will require a long time to effect even a partial cure because the disease is due to ignorance and the only cure for ignorance is a long-continued process of education. Radiology is a young branch of medicine but we frequently must recall the old aphorism that "Life is short, the art long." With some men life will always be too short to acquire even a moderate proficiency in the difficult art which is medicine, and what they call experience will be only a succession of repeated mistakes.

The only possible solution for our correspondent's difficulty is a continuous and patient program of education of our fellow-practitioners who do not appreciate the value and possibilities in the field of radiology. We have a profound confidence in the final triumph of truth. As the radiologist, year in and year out, demonstrates to his colleagues in other branches of medicine his ability to help to solve their problems, their patronizing attitude will gradually disappear and there will remain no question in their minds that the radiologist is an honored practitioner of medicine.

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# ANNOUNCEMENTS

## THE INTER-SOCIETY COMMITTEE FOR RADIOLOGY

The completed report of the Inter-Society Committee for Radiology is published in the April 30 issue of the *Journal of the American Medical Association*, page 1470. We regard this as an important activity in the work of the Committee, and urge all radiologists to study the finished report.

This report should be of some influence in protecting radiologists against unfair demands by hospital groups. The staff of the Bureau of Medical Economics deserves the commendation of all radiology for its straightforward and thorough appraisal of the situation.

Reprints of the report are available upon request to the Executive Secretary, Mr. Mac F. Cahal, 2561 North Clark Street, Chicago.

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## INSTRUCTIONAL COURSES

### NEXT ANNUAL MEETING, PITTSBURGH

One of the ideals of the Radiological Society of North America has always been to give as much instruction in modern radiological methods and clinical medicine as possible. This has been carried out by scientific papers, clinics, and scientific exhibits at our annual meetings. RADIOLOGY is our official printed effort in this direction and by original articles, editorials, and abstracts of the world's radiologic literature helps to keep our membership abreast of the latest developments in radiology.

This year, at the Annual Meeting, a further effort will be made in this direction. Definite courses of instruction, especially along fundamental lines, will be offered. You will recall that the need for such courses was suggested

by Dr. John D. Camp last year in his Presidential Address under the name of "Refresher Courses."

These courses will be similar to those given so successfully by the American Academy of Ophthalmology and Otolaryngology, that devotes approximately half of the entire time of its meeting to these courses of instruction. The success of our courses this year will determine what place they will occupy in our future meetings.

These courses will be given during the entire day, Sunday, November 27, and from 8 A.M. to 10 A.M. on Monday, November 28. They will be under the direct supervision of the Publicity and Educational Committee, of which Dr. Lewis G. Allen is Chairman. The courses will be given by men of recognized ability and should prove to be of great value to those who are fortunate enough to be able to attend. Further details will be given later.

HOWARD P. DOUB, M.D., *President*

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EDITOR'S NOTE

With this new volume, a slight change is being introduced in the style of printing references in bibliographies, abstracts, etc.: first, the volume, in black face type; then the page, and lastly the date. In the first numbers of the volume, some references will be found in both the old and the new style. That is the Scotch in us—why go to the expense of resetting standing matter? Both styles are equally clear to the readers, we are confident, but we desire to conform closely to the style of the Cumulative Index Medicus, with which all of our readers are familiar.

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## BOOKS RECEIVED

Books received are acknowledged under this heading, and such notice may be regarded as an acknowledgement of the courtesy of the sender. Reviews will be published in the interest of our readers and as space permits.

THE RADIOLOGY OF PULMONARY TUBERCULOSIS. By J. E. BANNEN, M.D., Ch.B., D.M.R.E., Hon. Radiologist, Hull Royal Infirmary; Radiologist, Hull Corporation Hospitals and Tuberculosis Clinics, Hull Corporation Mental Hospital, Willerby, Hull and Sculcoates Dispensary. A volume of 156 pages, with 39 illustrations. Published by William Wood & Company, Baltimore, 1938. Price: $4.50.

PRAXIS UND ERGEBNISSE DES KURZWELLENHEILVERFAHRENS BEI ALLGEMEINTHERAPEUTISCH RESISTENTEN ERKRANKUNGSFORMEN (Review of Short Wave Therapy). By DR. L. H. STIEBÖCK, emer. polikl. Assistent, ehemaliger Chefarzt des chirurgischen Spitales des Deutschen Ritterordens in Friedau. Reprinted from "Ergebnisse der gesamten Medizin" (Review of General Medicine), Volume 22, 1937–1938. Edited by Dr. Th. Brugsch, vordem Direktor der medizinischen Klinik der Universitat Halle a.d.S. Published by Urban & Schwarzenberg, Berlin.

TRAITÉ D'ÉLECTRO-RADIOTHÉRAPIE (Treatise of Electro-radiotherapy). By L. DELHERM, Electroradiologiste des Hôpitaux de Paris, Chef du Service central E. R. de l'Hôpital de la Pitie (Paris), and A. LAQUERRIÈRE, Electroradiologiste des Hôpitaux de Paris, Professeur à l'Universite de Montreal (Canada). Editors: H. Morel-Kahn, Electroradiologiste des Hôpitaux de Paris, Chef adjoint du Service central E. R. de l'Hôpital de la Pitie (Paris), General Secretary: H. Fischgold, Assistant d'Electroradiologie des Hôpitaux de Paris (Hôpital de la Pitie), Assistant Secretary. Two volumes consisting of 2,018 pages with 450 figures. Published by Masson et Cie, Paris, 1938. Price: 480 fr., cloth, bound.

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## BOOK REVIEWS

CLINICAL ROENTGEN THERAPY. Edited by E. A. POHLE, M.D., Ph.D., F.A.C.R., Professor of Radiology, Chairman, Dept. of Radiology and Physical Therapy, University of Wisconsin. Foreword by GEORGE W. HOLMES, M.D., Professor of Roentgenology in Harvard Medical School, Boston. A volume of 819 pages, illustrated with 199 engravings and a colored plate. Published by Lea & Febiger, Philadelphia, 1938. Price: $10.00.

In this volume, a complement to "Theoretical Principles of Roentgen Therapy," Pohle has edited a series of chapters written by recognized experts on the various clinical phases of roentgen therapy with the idea of offering to the radiologist helpful advice and suggestions in his daily work and to offer to the beginner a guide in the treatment of those conditions which have been found to be amenable to radiation. For these reasons the book is a practical one, and, as Holmes points out in his Foreword, until Dr. Hickey and Dr. Pohle undertook the production of this text, no serious attempts had been made to write a comprehensive text-book on roentgen therapy in English.

As one casually thumbs through this book, first noting the imposing list of contributors, then the space devoted to each of the chapters

on treatment, glances at the illustrations, and eyes over the bibliographies, one feels that here indeed must be the solution to the long-recognized need of a worthwhile text on radiotherapy. I must admit that after carefully and critically reading this book my offhand opinion about its excellence was well confirmed. The method of presentation of the subject matter by the various authors is admirable—in fact, exemplary. Pohle has edited these various chapters wherever it seemed to have been indicated, and to the composite practically nothing can be added. One ponders in vain to invent an improvement in the whole setup of this volume. In summary, having conscientiously read this book and many others of the same general purport and having reviewed them in this and other journals, I would only state that since this is almost my ideal of a text on radiotherapy I can recommend it without the slightest reservation as the best text on radiotherapy.

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ANALES DEL CENTRO DE INVESTIGACIONES FISIOLOGICAS. (For the year 1936.) Edited by PROFESSOR ROQUE A. IZZO. A paper of 526 pages, with numerous illustrations. Buenos Aires: Pabellon "Las Provincias," Hospital Tornú, 1937.

This volume is a collection of papers from the workers in the Institute of Professor Izzo, in Buenos Aires, and it presents their experiences with various aspects of tuberculosis. Therefore, it merits the serious attention of those whose work lies in any of the many fields of this disease. Because of the space necessary to do so, it seems impossible to abstract or criticize the many chapters in this volume. It is suggested, therefore, that it be consulted in the original, an easy task, because each chapter is summarized in Spanish, English, German, and French.

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# IN MEMORIAM

## ROBERT HUGHES MILLWEE, M.D.

Word has been received of the death of our fellow-member, Dr. Robert H. Millwee, whose home has been in Dallas, Texas. His wide experience and scientific attainments have made him known, however, far beyond his immediate locality, and he was an honored member of many medical and scientific societies beside the Radiological Society of North America.

A fitting sketch of Dr. Millwee's career is being prepared for the next issue.

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## ANEURYSM

Left-sided Bronchial Carcinoma or Aortic Aneurysm? Alexander Strubell-Harkort. München. med. Wchnschr., Feb. 4, 1938, **85,** 177–179.

A case report of a locksmith in whom, on the basis of an anterior roentgenogram and a kymogram of the chest, a diagnosis of aortic aneurysm was made. At another institution a diagnosis of tumor was made and verified at necropsy. The author points out some of the difficulties involved, but apparently he does not consider the value of oblique and lateral views important enough for mention.

L. G. JACOBS, M.D.

## ANIMAL EXPERIMENTATION

The Effect of Roentgen Rays on the Erythropoiesis. K. Mardersteig. Strahlentherapie, 1938, **61,** 107.

Rabbits were given total body exposure to roentgen rays produced at 180 kv., filtered through 0.5 mm. Cu. The F.S.D. was 1 meter up to 100 r and 50 cm. for doses over 100 r. Single doses of 50 r showed a temporary stimulation of the bone marrow. Doses of 250 r produced a brief stimulation, followed by an inhibition of the bone marrow function, after which came regeneration. This initial stimulation is not observed if a single dose reaches 600 r. After doses of from 3,000 to 6,000 r, the bone marrow ceases to function. Daily exposure to small doses continued for weeks led to the same picture as observed during fractional roentgen therapy in man. Following initial stimulation, the erythropoietic function is inhibited; then follows regeneration of the bone marrow. Irradiation of blood samples *in vitro* with doses of 50, 100, and 300 r did not show any effect on the reticulocytes, while doses of from 500 to 1,000 r definitely inhibited the development of the cells.

ERNST A. POHLE, M.D., Ph.D.

## THE BLOOD

X-ray Treatment of Blood Diseases. J. Ducuing, P. Marques, and O. Miletzky. Jour. Radiol. Electrol., June, 1937, **21,** 250. (Reprinted by permission from British Med. Jour., Oct. 9, 1937, page 55 of Epitome of Current Medical Literature.)

The authors have treated by means of total radiotherapy 11 cases, of which there were five of Hodgkin's disease, five of myeloid leukemia, and one of lymphatic leukemia. They irradiated the whole body by means of two x-ray tubes energized simultaneously. They gave a total maximal dose of 300 r units in from three to four weeks; the maximum dose at a sitting was 25 r units, and the applications were given every second or third day. During the course of treatment the blood should be closely watched, as the danger of the treatment lies in the possibility of causing a leukopenia or thrombopenia rather than an anemia. Leukopenia usually does not arise in lymphogranulomatosis and in leukemia. The anemia which is always present in these cases does not constitute contra-indication to total radiotherapy; in fact, it is often improved by the treatment. Thrombopenia is more serious, and no cases showing less than 100,000 thrombocytes per cm. should be subjected to the treatment. Cases of lymphatic leukemia are particularly prone to develop anemia and leukopenia as a result of the treatment.

## CANCER (DIAGNOSIS)

Sedimentation Reaction in Different Forms of Cancer, Especially with Regard to its Prognostic Value: Cancer of Breast. P. Jacoby and J. Spotoft. Hospitalstid., July 6, 1937, **80,** 811–813. (Reprinted by permission from British Med. Jour., Oct. 23, page 64 of Epitome of Current Medical Literature.)

Since 1932 the authors have systematically applied the blood sedimentation test to the patients attending the radium station in Odense, Denmark. This test was employed not only before and during x-ray and radium treatment, but also at the half-yearly or yearly follow-up examinations. Evidently a high sedimentation rate in cancer depends chiefly on the parenteral absorption of proteins derived from inflammatory reactions and necroses of newgrowths, and not on their actual size or rate of growth. The sedimentation test is, therefore, of little value in diagnosis or differential diagnosis. In the authors' experience it is of great prognostic value. Putting the limit between the normal and a high sedimentation rate at 15, they applied this test to 59 cases of cancer of the breast before any treatment had been instituted, and they found that in the first stage of the disease this rate was almost invariably normal, whereas in the third stage it was normal in only seven and high in 15.

As the sedimentation test is apt to undergo considerable fluctuations during treatment, the authors have studied its behavior 12 months or more after the institution of treatment, and have found a remarkable difference according to whether the patient had or had not developed metastasis. Of 51 patients treated for cancer of the breast and subsequently showing no objective or subjective evidence of disease, the six who had been symptom-free for more than 60 months all showed a normal sedimentation rate; and the shorter the interval of freedom from symptoms between treatment and the sedimentation test the lower was the proportion of cases in which it was normal. Nearly all the patients developing metastases secondary to cancer of the breast showed a high sedimentation rate; indeed, among 39 patients with such metastases it was normal in only two. Hence the authors' conclusion that when the sedimentation rate is consistently high in a patient who has been treated for cancer of the breast, the prospects of recurrence of the disease are great.

## CANCER (THERAPY)

The Treatment of Cervix Carcinoma in the Small

Hospital. G. Frommolt. München. med. Wchnschr., Feb. 18, 1938, **85**, 241, 242.

Due to various imperfections in the staff and equipment of small hospitals, the author prefers operation for operable cases. He discusses the results after various operations. The fact that he reports operative mortalities ranging from 6 to 50 per cent for various operations is, in itself, sufficient commentary.

L. G. JACOBS, M.D.

## DIABETES

Functional Irradiation of the Hypophysis: Insulin-resistant Diabetes. L. Delherm and H. Fischgold. Bull. et mém. Soc. de Radiol. méd. de France, October, 1937, **25**, 611–619.

There are many cases of diabetes, particularly those associated with other syndromes such as acromegaly and Basedow's disease, which become, it appears, resistant to insulin. These cases can be given enormous quantities of insulin without relief of symptoms. The authors find that in many of these cases irradiation of the hypophysis reduces the tolerance to insulin to a point at which the cases can be carried along comfortably on small or moderate amounts. They discuss the relationship of the pituitary to diabetes. They believe that one of the secretions of the pituitary certainly counteracts the influence of insulin and that a reduction of this activity results in a diminished requirement for insulin in diabetics. The dosage given varies from 1,200 r, given to three portals, to 4,000 r, given to three portals. The results have been very satisfactory in reducing tolerance to insulin and they regard this markedly increased tolerance as an indication for radiotherapy of the pituitary region. They warn that immediately after the discontinuance of irradiation there are apt to be rather grave symptoms. The method is preferable to surgical intervention.

S. R. BEATTY, M.D.

## GALL BLADDER (NORMAL AND PATHOLOGIC)

Fractional Oral Cholecystography. J. Masson. Jour. de radiol. et d'electrol., November, 1937, **21**, 494–498.

Cholecystography is a valuable addition to the armamentarium of those interested in diagnosis of abdominal conditions. In the author's experience the fractional oral method has given excellent results, and he feels that routine intravenous cholecystography is unnecessary and should be used only after oral cholecystography has failed.

S. R. BEATTY, M.D.

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Doryl Merck (the Hydrochloride of Carbaminoylcholine Ester) as a Means for Initiating a Gallbladder Contraction. Paul Grüneis. München. med. Wchnschr., Feb. 4, 1938, **85**, 181–183.

In order to do a gastro-intestinal study and cholecystography the same day, the author tried to obtain gallbladder contraction by some agent administered parenterally. Such an agent was Doryl. Contraction occurred in all cases in which it could be induced by a fat meal. The dose was 0.25 mg. of active substance. The contra-indication is any condition in which a sudden marked fall of blood pressure is dangerous, as in cardiac decompensation, Stokes-Adams syndrome. Untoward reactions were not observed. By inserting duodenal sounds, almost pure bile could be obtained by this drug.

L. G. JACOBS, M.D.

## HEMOPTYSIS

Radiology of Hemoptysis. W. Schmidt and K. Unholtz. Ztschr. f. Tuberk., **78**, 1–24. (Reprinted by permission from British Med. Jour., Oct. 9, 1937, page 55 of Epitome of Current Medical Literature.)

Schmidt and Unholtz have x-rayed 151 cases of hemoptysis, mostly of tuberculous origin. The patients were filmed in bed immediately following cessation of bleeding, and again later when convalescent. In one-third of the cases no clinical or x-ray changes could be found. In the remainder shadows due to massive aspiration of blood or secondary inflammatory changes were seen. They were of considerable assistance in determining whether the underlying condition was in the process of healing, stationary, or progressive. Evidence of hematogenous dissemination of tuberculosis was well marked. By means of roentgenograms it was possible to ascertain the course of the disease, its distribution, and the course of the focal pneumonias following hemoptysis, even in the absence of physical signs. Changes of non-tuberculous origin were differentiated only by the absence of the specific organism.

## INFECTION

Pseudo-cancer of Recto-sigmoid of Amebic Origin. Uzac and L. Timbal. Arch. d. mal. de l'app. digestif, November, 1937, **27**, 986–988.

The authors report a case of pseudo-cancer caused by infection with *B. melitensis*. Both the radiologic and proctoscopic examinations gave the appearance of cancer in the judgment of the investigators.

S. R. BEATTY, M.D.

## INFLAMMATORY DISEASE

Roentgen Therapy of Inflammatory Disease. L. Freund. Strahlentherapie, 1937, **60**, 19.

In a more or less historical sketch the author points out that he was one of the first radiologists to recognize the benefit of small doses of roentgen rays on the healing of wounds and on inflammatory processes. In the first instance he feels that the connective tissue is stimulated; on the other hand, large doses may prevent the formation of keloids in surgical incisions in individuals with such a tendency. The author assumes a very generous attitude regarding his priority. To him it is more important that his original observations have

been generally accepted, even though they had to be "rediscovered" several times.

ERNST A. POHLE, M.D., Ph.D.

## THE INTESTINES

Functional Disturbances of Small Intestine: Causes, Results. A. Krafft. München. med. Wchnschr., Sept. 17, 1937, **38**, 1488–1490.

The author is strongly of the opinion that a considerable quantity of the gas noted in the small intestinal tract is actually not resultant of an obstruction, but rather, causative. A gas bubble can act as a foreign body, causing disturbance in the passage of the fecal column. There is always considerable gas in the small intestinal tract—either swallowed air or gas formed therein—which is quickly absorbed by the bowel and excreted by the lungs. It is common knowledge that hunger, laxatives, and enemas increase the gas content of the intestines. A preliminary examination of the abdomen affords a fair index as to the degree of gas content. The author suggests a photo-electric cell measurement of the fluorescent screen, using thickness and weight of patient as an indicator of percentage of gas content of the bowel.

Heretofore it has been assumed by most observers that gas in the intestinal tract, particularly in the small intestines, is always indicative of some bowel disturbance rather than a cause thereof. Thus, in peritonitis intestinal pneumatosis is explained on the assumption of paralysis of the gut. In every intestinal disturbance the mucosa is somewhat affected, causing a disturbed absorption of gas. But it can be demonstrated how in certain cases a trapped air bubble can hinder passage of a barium meal, provoking increased peristalsis proximal thereto. Depending upon its intensity or duration, it can cause either increased gastric emptying or, strangely, gastric dilatation with retention. This phenomenon has been repeatedly observed in post-infectious gastro-intestinal complaints, *viz.*, pneumonia, in which case ileus has been suggested; also in gastro-enteritis, over-exertion, dreams, and acute toxic absorption. When meager physical signs and symptoms are present roentgenologically, the condition can be diagnosed, and these cases are frequently under the surgeon's observation for appendiceal disease, or the radiologist's survey for possible peptic ulcer.

From the author's vast experience, he rather dogmatically asserts that too often a peptic ulcer is diagnosed in the presence of mere indirect signs. Inasmuch as gas-ileus and gastro-duodenitis cannot be distinguished at times and are frequently associated, it makes it increasingly difficult to make a definite diagnosis even roentgenologically, unless this new entity is considered. Peptic ulcer and gastro-duodenitis are clinically and roentgenologically difficult to differentiate. The author considers many of the former diagnoses of ulcer as erroneous, if a niche was not demonstrated, and may be well accounted for by the admitted entities of lymphangitis mesenterialis, or gastro-duodenitis. The presence of trapped gas bubbles can be detected in the erect position in a surprising number of cases, and three typical layers are demonstrable.

The double test meal is advised by the writer, thereby detecting and rechecking the entity if suggestive, by any abnormal distribution of intestinal gas. The author considers gas in the upper small intestines as causative of symptoms as is the more frequently observed colonic and ileal gas. It seems rather incongruous to state that in the presence of a scaphoid abdomen, with no symptoms of meteorism, in the presence of gas in the small intestines, this may be a normal finding.

In summation, the author states that in many thousand gastro-intestinal examinations he is convinced that one of the most frequent causes of acute and chronic dilatation and insufficiency of the stomach is probably resultant of gas-ileus, which can be diagnosed only roentgenologically.

W. M. STECHER, M.D.

## THE JOINTS

Roentgen Diagnosis and Therapy of Syringomyelia. E. B. Gurevitch, G. B. Fomin, and P. B. Shklovskaia. Am. Jour. Roentgenol. and Rad. Ther., September, 1937. **38**, 415–426.

Of 128 cases, 73 per cent showed trophic disturbances. The most frequent involvements were in the phalanges and joints (75 per cent), wrist (6.5 per cent), elbow (15 per cent), and shoulder (3.5 per cent). This discrepancy in location and frequency of bone changes, according to other authors, is due to failure of thorough skeletal study in these patients.

Both productive and destructive changes occur, the former minimal, as mushroom-like spreading or sharpened edges of the distal phalanges. The destructive changes may be slight to marked. Various types may occur in one patient and do not necessarily parallel the clinical symptoms. Dislocations, ankylosis, small or large bone deposits may occur in or outside of the joint. Fractures frequently occur, at times unbeknown to the patient. These are usually transverse fractures and are united by large amount of callus that extends considerably beyond the fracture, either scattered or smooth spindle-shaped.

Radiation treatment resulted in undoubted improvement in 68.6 per cent; there was no change in 30.9 per cent; one patient grew worse. The roentgen prescription was: 185 kv., 4 ma., 0.5 mm. Zn plus 3.0 mm. Al filter. This was applied in 50 per cent erythema doses through 8 × 15 cm. fields, over and moderately beyond the involved area of the spinal cord, in seven or eight seances, one per month. Sensory improvement was the most frequently noted, next in percentage followed increased muscle power, disappearance of pain, improved motor function, diminution of parasthesia, and diminution of atrophy. The biologic reason for improvement by radiation is probably a diminution of the glial hyperplasia and thus diminution of the pressure on the nerves.

S. M. ATKINS, M.D.

Unilateral Micrognathia: A Rare and Interesting Congenital Deformity. Castay. Bull. et mém. Soc. Radiol. Méd. de France, February, 1937, **25**, 125, 126.

The author presents a case of unilateral micrognathia involving both the superior and inferior maxillæ on the right in an 11-year-old girl.

There is partial ankylosis of the temporo-mandibular joint, the patient being able to open her mouth only 1 5 cm. The lesion is probably congenital.

S. RICHARD BEATTY, M.D.

## THE KIDNEYS

Radiation Therapy of Tumors of the Renal Parenchyma in Adults. Archie L. Dean, Jr. Jour. Urol., March, 1938, **39**, 303–313.

The following criteria of external irradiation in tumors of the renal parenchyma in adults may be used by urologists: (1) External irradiation alone cannot be relied upon to cure these tumors; (2) pre-operative irradiation will probably decrease the size of these tumors; (3) external irradiation will not make an inoperable tumor operable; (4) pre-operative irradiation may practically prevent the dissemination of tumor cells during a nephrectomy; (5) metastasis may occur while waiting for the full radiation effect of pre-operative irradiation; (6) if a renal tumor is only partially removed, post-operative irradiation may slow the recurring growth but will not stop it; (7) there is a great difference in the radiosensitivity of metastasis.

Using 200 kilovolt units the following pre-operative cycle is suggested: three skin portals, anterior, lateral, and posterior, each about 10 by 14 cm. in size; a target-skin distance of 70 cm.; filtration of 2 mm. of copper; a daily dose of 250 r to a skin portal, and, with the portals treated in turn, a total of 2,500 r to each portal. When this dose has been given, the region of the renal pedicle in a man weighing about 150 pounds will have received approximately five threshold erythema doses. If the patient is thinner, the tumor dose will be proportionately greater. This cycle consists of 30 treatments and requires about a month for completion. If nephrectomy is performed at the end of this time, there should be no appreciable delay in the healing of the wound.

Just before nephrectomy the function of the more normal kidney should be determined as well as the presence or absence of metastasis. In inoperable or post-operative cases a maximal tumor dose is required and the time required is not so important. Four portals are treated, and practically all of the skin covering the side of body at the kidney level is used. Each portal is irradiated once in four days, and 3,000 r may be given each portal. In a 150-pound man, the renal pedicle receives more than 7 T.E.D. This cycle may be repeated in favorable cases and after a suitable rest period. All factors of diagnosis, treatment, and end-results should be critically studied whenever radiating a tumor of the adult renal parenchyma.

JOHN G. MENVILLE, M.D.

Malignant Tumors of the Kidney in Children. Herman L. Kretschmer. Jour. Urol., March, 1938, **39**, 250–275.

A report of seven cases of Wilms' tumor. The tumor is characteristic in that it is essentially a disease of infancy and childhood; it runs a silent and rapid course; has a characteristic and unique histological picture; is generally fatal, and there is a multiplicity of theories regarding its pathogenesis.

A thorough review of the pathogenesis, symptoms, sex, diagnosis, and treatment is given. Deep x-ray treatment was given pre-operatively in five cases: a response was noted in all but one. All cases were given deep x-ray therapy post-operatively. Of the seven patients, two are living, three years four months, and two years six months, respectively; the remaining five patients are dead.

The majority of authors favor pre-operative radiation and nephrectomy in the treatment of Wilms' tumor.

JOHN G. MENVILLE, M.D.

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Calcification of Renal Tumors and its Relation to Prognosis. George F. Cahill and Meyer M. Melicow. Jour. Urol., March, 1938, **39**, 276–286.

A report of 12 cases of calcification in carcinomas of the renal parenchyma demonstrable by x-ray and pathologic study. There were two additional cases not operated upon. It is estimated that 15 per cent of the above tumors present calcification. The authors are of the opinion that a hemorrhage, necrosis, and calcification in parenchymal carcinomas are frequently associated with or are followed by metastatic dissemination. Their results indicate that the prognosis of tumors with calcification is less encouraging than of those without calcification.

JOHN G. MENVILLE, M.D.

## THE KNEE JOINT

Cure of a Bilateral Osteochondritis Dissecans of the Knee. P. Decker. Schweiz. med. Wchnschr., March 5, 1938, **68**, 221–223.

The evolution of this disease is in two periods. The first is symptomless, and if perchance roentgenograms are taken, they show a radiolucent spot in the bone under the articular cartilage, with a radiopaque spot in the center. Anatomical examination at this stage shows marked changes in the articular cartilage with detachment from the subjacent bone. A cavity with a piece of more or less detached bone beneath this accounts for the roentgen appearance.

In the second stage the piece of bone is discharged into the joint as a loose body. The lesion is most common in the knee on the external aspect of the internal condyle a little behind the inferior pole. The best roentgenograms are thus obtained with the knee slightly flexed. The lesion is sometimes bilateral. Other joints may be involved.

Three theories of origin are considered; arterial embolus, trauma, and constitutional defect. While none of these is very well substantiated, a case in which complete anatomical cure occurred favors a traumatic origin. Such a case, in a boy 14 years of age, is reported, spontaneous recovery in both knees from such a lesion over a period of about 20 months being observed.

L. G. JACOBS, M.D.

## LYMPHATIC SYSTEM

Congenital Lymphatic Diseases—Lymphangiomas. A. O. Singleton. Ann. Surg., June, 1937, **105,** 952–968. (Reprinted by permission from British Med. Jour., Aug. 21, 1937, page 29 of Epitome of Current Medical Literature.)

Singleton divides lymphangiomas into three types: simple or capillary, cavernous, and cystic. The first of these occurs superficially, and is easily diagnosed and removed. Cavernous lymphangiomas consist of a framework of connective tissues in which there are numerous single and communicating lymphatic cysts. There are also many anastomosing channels, irregular masses of lymphocytes, lymph nodes, and lymph follicles. These tumors are found in the neck, axilla, and groin, and may be so extensive that their removal necessitates major operation. Cystic lymphangiomas are tumors with larger, thin-walled, convoluted cysts filled with lymph and lymphatic fluid. They are commonly found in the neck, and may be present for some time before they enlarge. Lymphangiomas may be found in any part of the body; the most formidable are those within the abdomen, both retroperitoneally within the mesentery of the intestines and in the omentum. In these cases intestinal obstruction is a common complication. Because of the dysfunction of the lymphatic chain, infection is a serious development as it spreads rapidly through the connecting cysts. There are also communications between the cysts and venous radicles, and a blood-stream infection may develop. Excision is the usual method of treatment, and it may be difficult owing to the extent of the process. Radiation, either alone or in conjunction with surgery, is of value. Details are given of 28 cases; operative treatment was carried out in all but two instances, in which radiotherapy alone was applied. In nearly every case recovery took place, and there was a very low percentage of recurrence.

## NEURALGIA

Dental Trigeminal Neuralgia. W. Bauer. Wien. klin. Wchnschr., May 22, 1937, **50,** 681, 682. (Reprinted by permission from British Med. Jour., July 10, 1937, page 5 of Epitome of Current Medical Literature.)

The author distinguishes between true trigeminal neuralgia and the neuralgia caused by dental affections, although this may in its later stages simulate the true trigeminal neuralgia. The main causes of the dental type are chronic inflammatory conditions of the dental pulp and of the paradental tissues. These affections may give rise to changes in the Gasserian ganglion. In all cases of trigeminal neuralgia a thorough examination of the teeth and jaws is indicated, particularly by means of radiology. The dental trigeminal neuralgia usually subsides after the affected teeth have been attended to; on the other hand, a very severe trigeminal neuralgia may follow a dental operation in an otherwise healthy patient. These neuralgias, however, are usually cured in from three to fourteen days; x-ray treatment combined with aconitine therapy may be of value.

## THE NOSE

X-ray Visualization of the Naso-lachrimal Duct. George E. Hourn. Ann. Otol., Rhin., and Laryngol., December, 1937, **46,** 962–975.

The author describes the anatomy of the naso-lachrimal apparatus in considerable detail. X-ray visualization of the duct may give valuable information in many cases and is necessary, particularly, when operative procedures are contemplated. Beside the usual views in the lateral and Waters positions, he recommends an intranasal film. For this purpose an ordinary dental film is cut down to make a film pack about 2 × 4.4 cm. The nasal chamber is cocainized and the turbinates shrunk with epinephrin. The film is inserted into the nasal cavity so that the anterior border extends at least 5 mm. anterior to the ventral extremity of the middle turbinate, and with the base of the film over the second bicuspid to the second molar teeth. Lipiodol or lipiodol diluted with olive oil is used as the opaque medium. It is injected into the punctum, using a No. 24 gage needle after cocainizing the conjunctival sac. In cases with stricture or obstruction of the duct the lower end can be visualized by injecting the oil through the nasal ostium; the technic for doing this is described. Exposures should be made as soon after injection as possible. In exposing the intranasal film the central ray should be directed to pass slightly anterior to the dense superior lateral portion of the superior oblique orbital margin near the zygomatico-frontal suture, medially and caudally at an angle of 25° to the lower end of the lachrimal fossa.

L. W. PAUL, M.D.

## PAIN

Physiotherapy of Pain (General Considerations). L. Delherm and H. Fischgold. Jour. de radiol. et d'electrol., November, 1937, **21,** 503–505.

The authors consider the physiology of pain and point out that efficacy of electro-radiotherapy, including x-ray therapy, is limited to the peripheral neurone. The mechanism of pain relief from x-ray has not been explained, but the effect is believed to be due to a change

in the state of polarization of the neurone. Pain arising at levels above the spinal ganglia and their paths is little influenced by any type of physiotherapy.

S. R. BEATTY, M.D.

## PHYSICAL THERAPY

Subcutaneous Emphysema Associated with Perforated Peptic Ulcer. Horace McCorkle and Jean Stevenson. Surg., December, 1937, **2**, 930–936.

Subcutaneous emphysema arising from injuries to the chest or respiratory passages is a frequent occurrence, but emphysema arising from the gastro-intestinal tract is unusual.

A case is described in which air (gas) was found beneath the diaphragm, over the chest wall on both sides, and in the tissue of the neck following rupture of a hollow abdominal viscus. Various theories are given as to how the gas reaches the subcutaneous tissue from the peritoneum, namely: (1) By diffusion through the parietal peritoneum; (2) by extension along the esophagus and mediastinum to the neck; (3) by extension to the retroperitoneal areolar tissues and thence to the posterior mediastinum. The authors conclude that there is no satisfactory explanation.

J. E. WHITELEATHER, M.D.

## PERITONEAL CAVITY

The Radiological Study of Acute Abdominal Syndromes: Gaseous Distention of the Peritoneal Cavity. L. Bérard and P. Ponthus. Bull. et mém. Soc. de Radiol. méd. de France, October, 1937, **25**, 657–662.

It must not be forgotten that there are cases in which the peritoneal cavity rather than the visceral cavities is distended with gas, giving an appearance not at all similar. Peritoneal distention is differentiated from pneumoperitoneum by the gross amount of free gas. The etiology varies. Several case reports are included by the authors, illustrating cases of peritoneal distention, in one of which the cause for the condition was not found. In all cases of acute abdomen without an established diagnosis, radiography is indicated.

S. R. BEATTY, M.D.

## PNEUMOTHORAX

Spontaneous Pneumothorax. M. R. Castex and E. S. Mazzei. Arch. méd.-chir. de l'App. Respir., 1937, **12**, 23–38. (Reprinted by permission from British Med. Jour., Aug. 7, 1937, page 21 of Epitome of Current Medical Literature.)

The authors point out that spontaneous pneumothorax may often appear in cases of pulmonary tuberculosis. The condition usually occurs in young men under the age of 30; in the authors' 12 cases, in all of which recovery took place, there were no women. Benign spontaneous pneumothorax may arise when the patient is at rest or as the result of varying degrees of physical effort. The onset may be insidious or sudden, and the outstanding symptoms are pain and dyspnea, with palpitations, cold sweats, cyanosis, nausea, and vomiting. The intensity and duration of the pain is variable, and it may be localized or radiating. There is usually immobility of the affected side of the chest with diminution or absence of local fremitus, increased resonance, and loss of breath sounds. Radiology is of diagnostic value, as it establishes the extent of the pneumothorax and the degree of pulmonary collapse. The pneumothorax is usually complete when there are no adhesions present. Prognosis is good, the symptoms decreasing in intensity after a few days, and the patient recovering completely by the end of a month. The chief complications are hemorrhage and the simultaneous occurrence of the condition on both sides. Recurrence takes place in from 10 to 20 per cent of cases, in occasionally as often as 14 times. Treatment consists of complete rest, morphine injections to relieve pain, and slow respiration. In cases of circulatory shock stimulants may be necessary, and if acute anoxemia is present it is best to carry out extraction of the air and give oxygen.

## THE PROSTATE

Prostatic Enlargement. G. H. Schneider. Med. Welt, May 15, 1937, **11**, 679–681. (Reprinted by permission from British Med. Jour., Aug. 14, 1937, page 27 of Epitome of Current Medical Literature.)

The author ranges himself on the side of other German writers who have recently praised the x-ray treatment of prostatic enlargement, and he reports 24 successful cases. Beside avoiding the risks of narcosis and operative trauma, the preservation of sexual function is claimed. The dosage is worked out after pelvimetric measurements of sacro-prostatic, pubo-prostatic, and sacro-pubic sagittal distances. The application is in the form of 90 per cent of the erythema dose to a total of 350 to 500 r according to the focal distance chosen; preferably five fields of 10 by 15 cm., one perineal, two parasymphyseal, and two parasacral, are used. Before the benefit of the intensive irradiation is registered and the treatment is repeated (often two months), five or six weekly supplementary saturation applications are made, each of 50 to 100 r, from large, distant symphyseal or sacral fields. The treatment is to be combined at first with catheterization, and may cause a temporary increase in dysuria. The widespread opinion that advanced cases of prostatic hypertrophy are not radiosensitive is stated to be unfounded.

## RADIATION

Comparative Studies Regarding the Specific Effect of Roentgen Rays. G. Miescher. Strahlentherapie, 1938, **61**, 4.

The author investigated the effect of light, heat, roentgen rays, and thorium X on the skin of the ear of

guinea pigs and also on human skin. The following sources of radiant energy were used: quartz mercury vapor lamp, a quartz chamber through which was flowing water at the temperature of 50–51° C., roentgen apparatus (doses of 300–120,000 r), thorium X paint delivering alpha rays which were absorbed in 0.1 mm. thickness of tissue. Intensities of 150, 1,000, and 10,000 E.S.U. per c.c. were used. Histological studies were carried out on the excised skin specimen up to the fiftieth day after the application of these various agents. The early heat and light reactions are characterized by cell necrosis and disturbance of the mitosis (pyknosis). This reaction is non-specific and non-elective and appears first in the superficial cells. Regeneration starts within the first few days and is completed within two weeks. From the second to the fourth week numerous cells with double nuclei can be found. The reactions following exposure to roentgen rays and thorium X differ; there is no cell necrosis but only disturbance of mitoses. The late effect consists of abnormal karyokinesis, amitosis, polymorphism of nuclei, and hypertrophy of the entire cell. The principal effect of roentgen rays and alpha rays manifests itself in the nucleus and very little in the plasma; this explains the occurrence of cumulative late effects.

ERNST A. POHLE, M.D., Ph.D.

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The Reducing Effect of Roentgen Rays on Redox Dye Indicators. W. Seitz. Strahlentherapie, 1938, **61,** 140.

Dyes which belong to the group of Redox indicators are discolored when exposed to roentgen rays in a watery solution; the process is reversible. The author demonstrated this phenomenon with 17 different dyes. While this reduction process occurred without exception, oxidation can never be produced under any condition. The author discusses at length the mechanism of this phenomenon and considers its application to a hypothesis of the effect of radiation. In his opinion, part of the effect of roentgen rays is due to a reducing process, chemically speaking, which is caused by the electrons freed during irradiation.

ERNST A. POHLE M.D. Ph.D.

## RADIATION INJURIES

Cancer Developing in Accidentally Produced Radiodermatitis. S. Laborde. Rev. de Physiothérap., March-April, 1937, **13,** 89–99. (Reprinted by permission from British Med. Jour., July 24, 1937, page 15 of Epitome of Current Medical Literature.)

Laborde points out that although the occurrence of cancer in radiologists has long been known, cases of cancer formation following the therapeutic administration of x-rays are infrequent owing to the fact that patients are rarely subjected to graduated applications over a sufficiently long period. He reports four such cases occurring 11, 15, 18, and 21 years after treatment, in all of which histologic examination showed a spinomedullary epithelioma. The first case had had numerous applications over a period of four years for eczema of the hands, the second several applications for hair on the face, the third x-ray administration to the spinal column for paraplegia, and the fourth 15 applications over two years for facial angioma. The first patient was cured by amputation, the second by three applications of radium, the third is becoming worse in spite of radium therapy, and the fourth died. Laborde points out (1) that chronic radiodermatitis produced by whatever type or quality of irradiation is a precancerous lesion; (2) that although the causal factor after a long latent period was in each case x-ray administration, nothing is known of the nature of the phenomenon which suddenly produces malignant growth in tissues, modified in structure and physiology after so many years; (3) that cicatrization and cure may follow the application of radium provided that the cancer is surrounded by sufficient healthy tissue, for the radiosensitivity of cancers depends on the action of the rays on the neoplastic cells and on the medium in which they develop.

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Irradiation Sarcoma. Harwell Wilson and Alexander Brunschwig. Surg., October, 1937, **2,** 607–611.

Epidermoid carcinoma has been repeatedly observed in skin areas where there has been subcutaneous cicatrization, telangiectasis, and sometimes chronic ulceration due to previous irradiation with radium or x-rays. Irradiation sarcoma has not been frequently reported.

One case which was observed by the authors was a spindle-cell sarcoma developing after 90 x-ray irradiations had been given as treatment to some keloids above the right breast following a burn. Death from metastases followed.

The authors quote from various experimenters who were able to produce irradiation sarcomas in animals in chronically infected areas. They also have collected 25 cases from the literature, all arising from radiation to areas of chronic inflammation: 14 cases were due to treatment for bone and joint tuberculosis. The treatments in all cases were extended over a long period of time and the growths appeared in from three to 24 years.

J. E. WHITELEATHER, M.D.

## RADIUM

The Radiation Emitted by Blood and Other Tissues Following Radium Injections. Van Hove. Strahlentherapie, 1938, **61,** 300.

The author studied the radium content of the blood following intravenous injection of from 0.01 to 0.03 mg. by means of photographic films. In some cases the radium content dropped very rapidly on the fourth day: in others the drop occurred rather gradually. Even two months later there was still definite blackening of the film. Following subcutaneous injection of radium solutions the radium content of the blood reaches its peak 24 hours later. During the first few days following the injection the adrenals, bone marrow,

kidneys, spleen, liver, lungs, pancreas, and uterus contain radium. Several weeks later it is still found in the liver, spleen, and bone marrow.

ERNST A. POHLE, M.D., Ph.D.

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Experiments Regarding the Indirect Ionization by Gamma Rays. H. Smereker and K. Juris. Strahlentherapie, 1938, **61,** 161.

Observations in the Wilson chamber indicate that ionization by x-rays and gamma rays of radium does not occur direct but *via* the photo and Compton electrons. The authors studied this phenomenon by means of an ionization chamber with very thin walls, using gamma rays of radium. By practically preventing the electrons formed in the filter of the radium and in the air space between radium screen and ionization chamber from reaching the chamber, he could show that the ionization current thus measured is reduced to about 5 per cent of the current measured by means of a chamber with thick aluminum walls.

ERNST A. POHLE, M.D., Ph.D.

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Further Results in Determining Radium Doses in r with the Photographic Method. H. Kirchhoff and K. Bartz. Strahlentherapie, 1938, **61,** 363.

The authors found the photographic method a valuable addition to radium dosimetry. (They described the procedure in detail in "Strahlentherapie," 1935, **54,** 462.) In order to imitate conditions existing in practice the measurements were carried out in rice phantoms. Some of the isodose curves obtained with the method are shown in the article. The authors urge the adoption of the r in radium therapy.

ERNST A. POHLE, M.D., Ph.D.

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Radium Therapy of Condyloma Acuminatum. J. Körbler. Strahlentherapie, 1938, **61,** 137.

The author reports a case of a 13-year-old boy who had a condyloma acuminatum of fairly large size on the penis. The author prepared a radium mold which carried 12 radium screens at 1 cm. distance from the skin: six contained 3 mg. and six contained 2 mg., each filtered through 1.0 mm. Pt. The applicator was left in place for 93 hours, giving a total dose of 2,790 mg.-hr. Photographs show the patient before and two months after the treatment. The result was apparently very satisfactory.

ERNST A. POHLE, M.D., Ph.D.

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Studies Regarding the Problem of Radium Poisoning. K. Inouye and A. Krebs. Strahlentherapie, 1938, **61,** 269.

In the third of a series of articles concerning radium poisoning, the authors furnish proof that, following administration of emanation, long-lived disintegration products are deposited in the organism. The organs of preference are bone, bone marrow, spleen, and liver. It appears that following the application of emanation in solution, radium salts find their way into the organism and are deposited there. The tolerance dose for various disintegration products, especially polonium, was determined and compared with the tolerance for roentgen rays.

ERNST A. POHLE, M.D., Ph.D.

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The Danger of Pyometrium in Radium Therapy: How to Avoid. Th. Nogier. Bull. et mém. Soc. de Radiol. méd. de France, October, 1937, **25,** 646–648.

The presence or formation of a pyometrium during radium therapy prevents the proper treatment of the uterine lesion. The radium is not in contact with the walls equally and some areas are over-dosed and some under-dosed. The author believes that pyometrium can be avoided by pre-operative vaccination, by drains which he has devised to be applied in conjunction with the radium, or by daily removal of the radium and cleansing of the apparatus.

S. R. BEATTY, M.D.

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Studies Regarding the Problem of Radium Poisoning. A. Janitzky, A. Krebs, and B. Rajewsky. Strahlentherapie, 1938, **61,** 254.

The authors continued their studies of radium poisoning and determined experimentally the radium deposits in the human body. By measuring the emanation with a specially constructed Geiger counter they were able to record the absolute amount of radium deposits, the distribution in the various tissues of the body, and the emanation emitted. It appeared that very small amounts of radio-active substances, as little as 1$\mu$ gram in the body, may suffice to produce irreparable damage. This can be explained by the intense biologic effect produced by the alpha rays which are totally absorbed as well as by the complete cumulation.

ERNST A. POHLE, M.D., Ph.D.

## RECTAL CANCERS

Five Cases of Cancer of Rectum Cured by Roentgen Therapy. E. Bandier. Ugesk. f. læger., July 1, 1937, **99,** 714–719. (Reprinted by permission from British Med. Jour., Oct. 9, 1937, page 55 of Epitome of Current Medical Literature.)

Bandier endorses with certain reservations the general opinion that the radiological treatment of cancer of the rectum is palliative rather than curative. At the Radium Station in Copenhagen, in the period 1931 to 1934, the admissions for cancer of the rectum numbered 142, but only nine of these cases were considered operable. In 125 cases x-ray treatment only was given, a supplementary colostomy being performed in a few instances. There were 43 deaths during the first year after treatment, 39 during the second year, 15 during the third year, eight during the fourth year, and three during the fifth year. None of the patients who died showed at any time signs of clinical recovery, and in almost every case the cause of death was cancer of the

rectum. In the eight cases in which the immediate cause of death was other than cancer, the tumor of the rectum showed no regression. The author gives details of five cases in which, after microscopical verification of the diagnosis, clinical recovery was achieved under treatment by x-ray therapy alone. The observation period was three years in two cases and five in three. An attempt was made to ascertain what were the factors governing the recovery in these five most exceptional cases, but they appeared to be quite ordinary instances of adenocarcinoma of the rectum. Recovery could not be ascribed to any novel departure from conventional x-ray treatment of cancer of the rectum. The author concludes that while x-ray treatment is incomparably inferior to operative treatment in operable cases, these five recoveries justify further close study of x-ray treatment for this condition.

## THE SHOULDER JOINT

Function of Shoulder Joint after Reposition of Old Luxation of Humerus. C. Van Staveren. Nederl. Tijdschr. v. Geneesk., June 26, 1937, **81,** 3035–3037. (Reprinted by permission from British Med. Jour., Sept. 11, 1937, page 38 of Epitome of Current Medical Literature.)

The author has treated ten cases of chronic dislocation of the shoulder joint in elderly patients, and obtained good results without operation. In all but one case, in which it was axillary, the dislocation was subcoracoid. The treatment consisted in replacement under an anesthetic by Cooper's traction method. All the cases were subsequently submitted to x-ray examination, and in only one was there any evidence of arthritis deformans.

## THE SPINAL CORD

Spinal Extradural Cyst and Kyphosis Dorsalis Juvenilis. Ralph B. Cloward and Paul C. Bucy. Am. Jour. Roentgenol. and Rad. Ther., November, 1937, **38,** 681–706.

Extradural cysts are believed to be evaginations of the arachnoid membrane and dura mater at the point of emergence of the spinal roots from the meninges, and produce rounded thoracic kyphosis with a spastic paraplegia. Roentgenologically, enlargement of the spinal canal and erosion of the vertebral pedicles are seen. Depending on the duration of the disease, the bodies also show thinning, especially the anterior corners, which may even be completely absent. The superior and inferior intervertebral borders are frayed and permit the nucleus pulposus to press into them.

Early removal of the cyst, which most commonly occurs in the lower thoracic region, will rapidly relieve the symptoms and stop further atrophy, but in the later stages no such definite relief can be expected.

Although kyphosis dorsalis juvenilis, unassociated with such cysts, may be due to venous congestion and stasis within the vertebral bodies, nevertheless, they should be considered as a possible cause.

The entire article should be read.

S. M. Atkins, M.D.

## THE STOMACH

A Large Diverticulum of the Fundus of the Stomach. M. E. Pierron. Bull. et mém. Soc. de Radiol. méd. de France, October, 1937, **25,** 649–652.

The author presents a case showing a large diverticulum of the fundus. He states that this is a rare finding in his practice. A discussion of the diagnosis is given.

S. R. Beatty, M.D.

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The Treatment of Inoperable Carcinoma of the Stomach. H. Regelsberger. Strahlentherapie, 1938, **61,** 201.

In the author's experience the single massive dose method proved to be unsatisfactory. He developed then a modified Coutard technic (180 kv., 4 ma., 1 mm. Cu; 200 r per hour) and applied if possible one single field, using cross-firing only for very large tumors. The total dose per area amounted to about 4,000 r which corresponded to approximately 3,000 r in the tumor. By comparing the statistics of 44 cases treated with the massive dose method with 35 patients treated with the fractional dose method a great improvement in the results could be noted; about 60 per cent of the second series responded favorably to treatment. In 22 cases a filter of 0.5 mm. Cu and consequently shorter exposure times was used; however, the end-results were less favorable than with the heavier filter. A combination with surgical measures, especially in combating hemorrhage and in suitable cases also serum therapy should be considered.

Ernst A. Pohle, M.D., Ph.D.

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Diagnostic Value of Gastric Lavage in Adult Patients without Roentgenographic Foci in Lungs. U. Gad. Nord. med. Tidskr., May 22, 1937, **13,** 815–818. (Reprinted by permission from British Med. Jour., July 10, 1937, page 5 of Epitome of Current Medical Literature.)

The author has undertaken gastric lavage on two consecutive mornings, using 300 c.c. of water, in 271 patients admitted to a Danish hospital for tuberculosis. All these patients presented no radiological evidence of active pulmonary tuberculosis. In as many as 34 cases tubercle bacilli were found by this means, and the patients were classified in five groups. Out of 97 patients in the first group who were admitted to hospital for observation, although the radiological picture was perfectly normal, there were 11 in whose stomachs tubercle bacilli were found. In the second group of 66 patients there was a history of pulmonary tuberculosis earlier in life, but the radiological picture showed no sign of active disease. The gastric lavage, however,

yielded tubercle bacilli in five of these cases. In the third group of 75 patients suffering from pleuritis there were 12 whose stomachs contained tubercle bacilli, although in none of these cases was there any radiological evidence of a tuberculous focus in the lungs. In the fourth group of ten cases in which the radiologic findings were indicative of hilus tuberculosis, but in which there was no sign of any infiltration of the lungs, there were as many as six whose stomachs contained tubercle bacilli. In the fifth and last group of 23 patients, representing a great variety of morbid conditions such as erythema nodosum, spontaneous pneumothorax, emphysema, bronchitis, etc., there was not one case in which gastric lavage yielded tubercle bacilli. Thus it was only in this last group that the radiologic and bacteriologic tests agreed in being invariably negative. The author concludes that the radiologic examination of the lungs often fails to detect active pulmonary tuberculosis, and that in many cases gastric lavage repairs this diagnostic failure.

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The Value of Gastroscopy in Diagnosis and Surgical Treatment of Chronic Gastroduodenal Ulcer. Rudolph Schindler. Surgery, November, 1937, **2,** 692–709.

Schindler points out that gastrophotography is not satisfactory in the diagnosis of ulcer because of the inability to identify the area upon the developed film and the fact that the most sensitive films do not satisfactorily differentiate yellow and red colors, so important in gastroscopy, especially in the diagnosis of ulcer. He considers gastrophotography worthless.

Roentgenologic examination is, on the whole, of greater value than gastroscopy in gastroduodenal ulcer, in contrast to carcinoma and chronic gastritis. Gastric ulcers are sometimes missed by roentgenoscopy, found by gastroscopy, and *vice versa*. Ulcers of the duodenum and of the pyloric canal cannot be seen by gastroscopy. However, a number of advantages of gastroscopy are given, including the demonstration of ulcers not diagnosed by other methods, the ability to follow healing of the ulcer, and the localization of gross hemorrhage.

W. A. SODEMAN, M.D.

## THE THYMUS

A Case of Hypertrophy of the Thymus Treated by Roentgen Therapy in 1911. Th. Nogier. Bull. et mém. Soc. de Radiol. méd. de France, October, 1937, **25,** 643–645.

The author presents a case which be treated in 1911 with fairly heavy doses of lightly filtered x-rays. There have been no untoward after-effects. The skin of the neck is absolutely normal.

S. R. BEATTY, M.D.

## TUBERCULOSIS (PULMONARY)

Vitamin C in Hemoptysis. F. Capelli. Riv. di pat. e clin. d. tuberc., May 31, 1937, **11,** 317–321. (Reprinted by permission from British Med. Jour., July 24, 1937, page 13 of Epitome of Current Medical Literature.)

The author has found ten daily intravenous injections of 50 mg. of ascorbic acid useful in certain hemoptyses due to pulmonary tuberculosis in a small series of patients. The method failed in two cases of hemorrhage accompanying a new extension of the tuberculous process, proved radiologically, but it appeared strikingly successful in the prevention of regularly recurring hemorrhages in cases of long-standing fibrosis with cavitation, and it seemed effective when other treatments failed in cases of frequent small hemoptyses in those having minimal pulmonary foci of infection. In phthisis there is little alteration of the blood coagulation rate, and the hemostatic action of vitamin C would appear to be attributable to a regulatory effect on adreno-cortical and anterior pituitary hormones, combined possibly with a catalytic action on clotting ferments.

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Systematic Fluoroscopy for the Detection of Tuberculosis in the French Army. J.-J. Didiée. Bull. et mém. Soc. de Radiol. méd. de France, October, 1937, **25,** 619–627.

Admitting that fluoroscopy is not as accurate as radiography for detecting early lesions, it has, however, become accepted as a routine method of case-finding in the French army. The convenience of the method, the relative lack of expense, and the rapidity with which large groups of men can be examined rather offset the slight loss of accuracy which can be expected. However, the employment of experienced radiologists and the association of this examination with rigorous clinical examination, produce, it is felt, a very great degree of accuracy in detecting cases of tuberculosis. Those cases in which there is any suspicion of a lesion are subjected to radiography. The technic of radioscopy and the system which has been developed for fluoroscopy of large numbers of men are described in some detail.

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Problem of Tuberculosis, with Special Regard to Question of Isolation. O. Lassen. Ugesk. f. Læger., June 10, 1937, **99,** 615–625. (Reprinted by permission from British Med. Jour., Aug. 21, 1937, page 30 of Epitome of Current Medical Literature.)

The author has undertaken an intensive study of the clinical histories of the last 100 patients who died of open pulmonary tuberculosis in the town of Aarhus, Denmark. The average age at death was between 31 and 32, and two-thirds were under 35. The clinical and radiological reports at the time when the diagnosis was first made showed in as many as 78 cases such advanced disease that little hope of recovery could be en-

tertained; and among the remaining 22 cases advanced, but still curable, disease was often found. A study of the institutional careers of these 100 patients revealed that as the disease progressed the duration of hospital or sanatorium treatment became longer, and as all the cases terminated fatally no permanent benefit could be claimed on their behalf for the institutional treatment they had received. Did it benefit the community by the limitations it imposed on opportunities for spreading the disease? The author is inclined to think that these patients did all the harm they could in this respect while they were still leading free and active lives. In Aarhus, 82 per cent of all the deaths from tuberculosis take place in hospital, and though this arrangement certainly ensures that the patients receive good nursing, the author wonders how valuable it is from the epidemiological point of view. He notes in this connection that while the tuberculosis mortality has recently declined in a most encouraging fashion, there is not a corresponding decline in the tuberculosis morbidity.

## TUMORS (DIAGNOSIS)

Roentgen Diagnosis in 94 Cases of Renal Tumor. E. Ross Mintz. Jour. Urol., March, 1938, **39**, 244–249.

A report representing pyelographic findings in 94 cases of renal tumor. The tumors were cortical in 82 instances, pelvic in nine, and extrarenal in three. Displacements and defects of the calyx, pelvis, and ureter are tabulated. It is stated that the roentgen picture was just a link in the chain of evidence in making a diagnosis of renal tumor. Equally important are the history and the clinical signs and symptoms.

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Adamantinoma of the Lower Jaw. R. Jaulain. Jour. de Méd. de Bordeaux, May 29, 1937, **114**, 693–703. (Reprinted by permission from British Med. Jour., Aug. 7, 1937, page 21 of Epitome of Current Medical Literature.)

Jaulain states that adamantinomas are very uncommon tumors, and are usually found in females over the age of 15. The adamantine epithelioma is most commonly situated on the posterior part of the horizontal ramus of the lower jaw. The first symptom is the gradual but steady increase in the size of the jaw, which causes a progressive deformity of the face. On palpation a fixed tumor can be felt; it may be hard, or, if cystic, fluctuation may be present. There are no functional symptoms in the early stages, and the general condition of the patient is good; diagnosis can be confirmed by radiography. The tumor, if neglected, may become as large as a fetal head, extending downward to the chin. Sometimes the teeth erode the palate and fall out, speech and mastication become difficult, and gradually the general condition declines as a result of toxic absorption. If the tumor is cystic, puncture will draw off a yellow or dark fluid, similar to that from an intracystic hemorrhage; while if it is hard, radiography will often show destruction of the adjacent bone. Treatment must aim at complete removal, and this may be carried out in the early stages, when the lesion is localized, by curetting. In the case of large tumors extensive resection is necessary in order to prevent recurrence. A careful technic is needed for this operation, but even then bronchopneumonia is liable to develop. A case is reported in which a large tumor was successfully removed, but the patient died from pneumonia on the thirteenth day. Emphasis is laid on the importance of early treatment while the prognosis is still good.

## TUMORS (THERAPY)

Roentgen Therapy of Tumors of the Hypophysis. J. Erdélyi. Strahlentherapie, 1938, **61**, 241.

The author relates his experience with roentgen rays in the treatment of hypophyseal tumors. During the last 12 years he has treated 40 cases of acromegaly and a recent survey showed that 22 patients are still well and pursuing their occupation. Since 1924, he has observed 61 tumors of the hypophysis: seven of these were operated on; four died shortly after the operation; two improved, and one was not improved. The remaining 54 cases were treated by irradiation: 12 died; 13 could not be traced; 13 remained stationary, and 16 were improved. He used 180 kv., 30 cm. F.S.D., 1 mm. Cu + 1 mm. Al, and single doses of 220 r. A temporal area is exposed as test field and if this is tolerated well the dose is increased in the following two days to 650 r. The other areas are an additional temporal field, one frontal, one parietal, and one occipital area. In this manner he administers approximately 100 per cent of the skin erythema dose to the tumor. In children this total dose is reduced to about 75 or 80 per cent. Care should be taken not to expose the eyes because injuries have been reported following excessive exposure. As a rule all cases are given x-ray therapy first unless intracranial pressure symptoms demand immediate operation. If the patient responds well to the treatment, additional series should be given at intervals of from six to eight weeks. All patients who are operated on should receive roentgen therapy later.

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Direct Irradiation of Cerebral Tumors. C. A. Elsburg, L. M. Davidoff, and C. G. Dyke. Bull. Neurol. Inst. N. Y., January, 1937, **6**, 19–32. (Reprinted by permission from British Med. Jour., Aug. 28, 1937, page 35 of Epitome of Current Medical Literature.)

The authors have made a preliminary report on the technic and results of the direct application of x-rays to cerebral tumors exposed at operation. Most of the tumors of the glioma group can be only partially removed at operation, their deep subcortical ramifications being untouched. Their sensitivity to x-rays varies enormous-

ly; the posterior fossa medulloblastomas of childhood give a response to deep x-ray irradiation after decompression, which appears to be better than removal, while in others, such as the astrocytomas and the glioblastomas, results are usually disappointing. With present methods not only is the liability to necrosis of the scalp and bone great but the tumor receives insufficient irradiation. In order to eliminate these disadvantages a very high voltage was used, and irradiation of irremovable and partially removable tumors was carried out in the operating theater by direct application of the rays to the cortex through a layer of cellophane. A 200,000-volt, 25 ma., oil-cooled apparatus was used, and an elaborate portable lead screen was arranged in the theater.

In order to establish the maximal safe dose experiments were carried out on monkeys. It was found that over 4,000 r units caused definite neuronal destruction, but 3,000 r units could be used with impunity. Both the cerebrum and cerebellum were irradiated, smaller doses being used for the former as it was found that cerebral symptoms were more readily evoked, although some of the symptoms were very late in onset. In some cases in which no cerebral symptoms occurred there was depilation and bone necrosis on the side opposite the point of entry of the rays.

In the application of this technic to man 18 cases of cerebral tumor were irradiated at operation, and although it is too soon to draw decisive conclusions, the method would seem to justify further trial and study.

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Status of Surgical and Irradiation Treatment of Wilms' Tumor, and Report of Two Cases. Walter H. McNeill, Jr., and Alexander J. Chilko. Jour. Urol., March, 1938, **39**, 287–302.

A review of Wilms' tumors and a report of two cases.

The first case was considered inoperable. Several x-ray treatments were given without noticeable improvement, and the child died in five months.

The second case, a 14-month-old child, was diagnosed clinically as having a Wilms' tumor, and was treated by x-ray alone. The mass gradually disappeared. During the past three years the child has received 10,319 r of x-ray, has gained $17^1/_2$ pounds, has a normal blood picture, and shows no skin reaction.

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Radiotherapy of a Mediastinal Tumor. M. Billant. Bull. et mém. Soc. de Radiol. méd. de France, October, 1937, **25**, 686–689.

The author presents a case with enormous mediastinal tumor treated in 1935 with x-rays. He comments on the use of roentgen rays in the treatment and in the differential diagnosis of mediastinal tumors.

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## ULTRA-VIOLET LIGHT

The Treatment of Peritoneal Tuberculosis by Ultra-violet Light. M. Aubert. Bull. et mém. Soc. de Radiol. méd. de France, October, 1937, **25**, 638–643.

The author presents 35 cases of peritoneal tuberculosis treated with massive doses of ultra-violet light. Out of these, 26 showed clinical cure, five were greatly improved although the full course of therapy could not be given, and four died. He believes that all cases of peritoneal tuberculosis with the single exception of those with pulmonary lesions should be treated with ultra-violet light.

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## THE WRIST

A Rare Anomaly of Ossification in the First Row of Carpal Bones. P. Reinbold. Schweiz. med. Wchnschr., March 5, 1938, **68**, 242.

A case report of a bilateral synostosis of the lunate and triquetrum, which produced no functional change in the wrist.

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